the
UNIVERSITY
of
TORONTO
MEDICAL
JOURNAL

MARCH 1967 VOL. XLIV NUMBER 5

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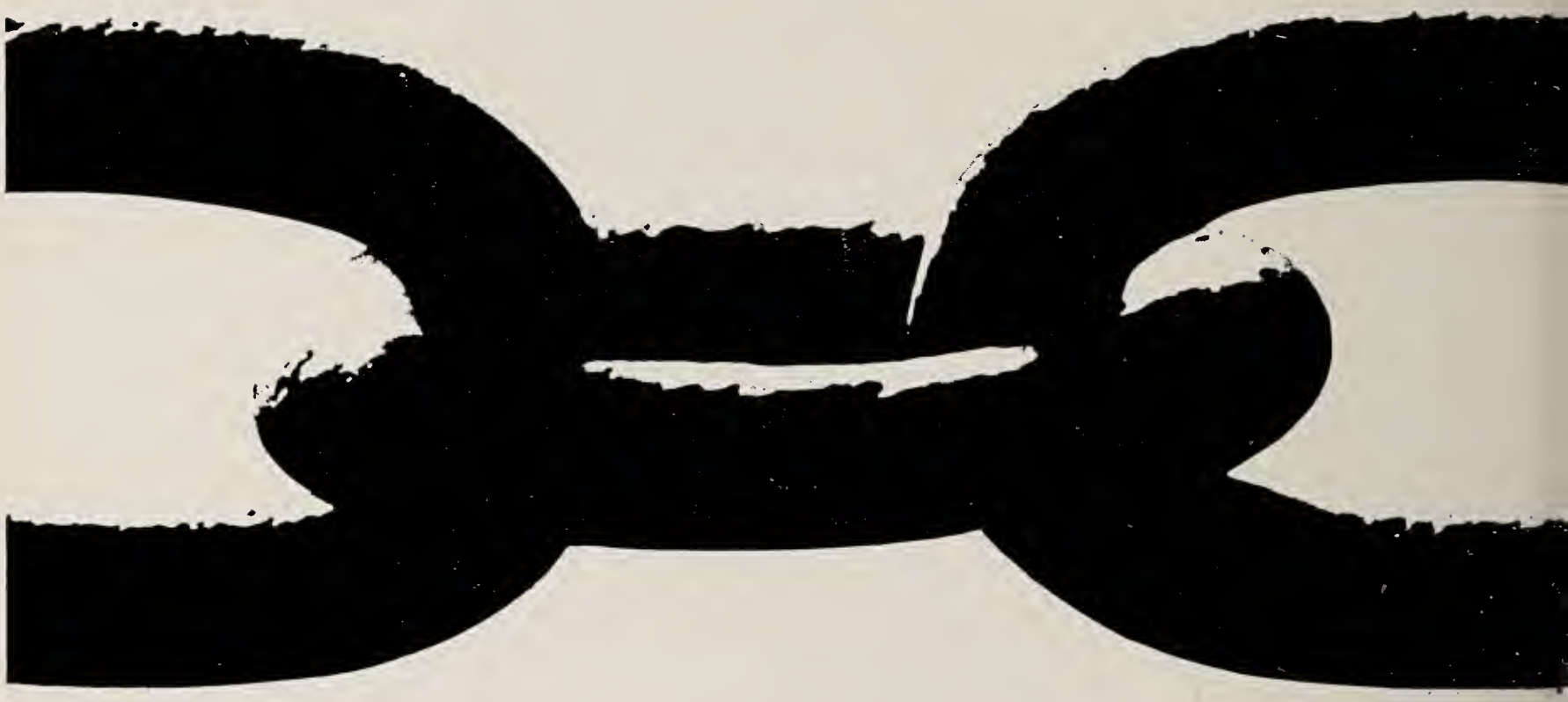

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the UNIVERSITY of TORONTO MEDICAL JOURNAL

Established December 1923
An Undergraduate Publication

Volume XLIV
Number 5
March 1967

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This Journal is published six times a year from November to April, by the Medical Society of the University of Toronto, to serve primarily as a medium for student expression.

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MANUSCRIPTS including references and footnotes should be typewritten double spaced on one side of the paper. Articles should not exceed 3,000 words. Canadian Press (American) spelling is to be used. References should be kept to a minimum, and should be cited numerically in order in which they appear in the text.

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CORRESPONDENCE should be addressed to: **Room 109,**
Medical Building,
University of Toronto,
Toronto 5, Canada.

Authorized as second class mail by the Post Office Department, Ottawa, and for payment of postage in cash. Printers: Maple Leaf Press, Toronto, Ontario.

Editorial

Neurophysiology is a tool—a sophisticated scientific attempt to understand nervous function. It uses such devices as electroencephalograms, digital computers, and implanted electrodes. Looking at similar phenomena, but from a different viewpoint, are psychiatry and psychology. When one is studying nervous function, there crops up the philosophical problem of what is "the mind". Western thought has traditionally divided the world into "mind" and "matter" or "psyche" and "soma", whereas Eastern thought considers "mind" and "form", and tends to ignore our concept of matter. Are mind and matter really different sides of the same coin? Can the criteria of matter accepted by neurophysiology be used to measure "mind" if the two are actually separate entities? Will we someday be able to equate thought and emotions to mathematical constructs or biochemical mechanisms?

Today, brain sciences employ powerful tools to understand nervous functions. Digital computers analyse in days data which would take months or years for men to handle. The new disciplines of cybernetics and communication theory are helping to create models of nervous processes. Inroads have now been made into the speculative fields of memory and learning with advances in neurochemical and psychological techniques.

We perceive our world through three dimensions and five basic sensations. Mathematics is able to describe the universe in many more than three dimensions. Our comprehension of "thinking" or the "mind" as well as other biological processes can only go as far as our tools permit. As Edmund Sinnott says, "The process of deduction is valid, but the results are only as true as the basic precepts are true."

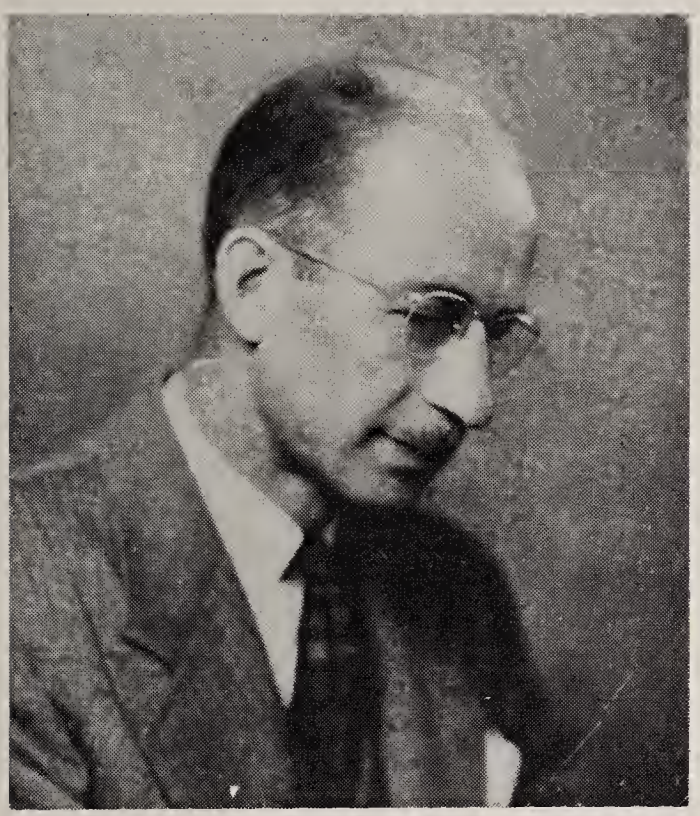
Let us indulge in some speculations into the future of neurophysiology. For example, a time may come, when instead of reading a book, one will mentally digest its contents by tuning into the proper computer channel and stimulating the appropriate cortical areas. *Brave New World* refers to theatres where one experiences—i.e. sees, feels, hears, tastes, and smells—an event. Why not? Dr. Wilder Penfield was able to evoke very real and lifelike memories and hallucinations by electrostimulation of the human cortex. Someday we may be able to arrange incoming stimuli to the brain with the help of chemicals and electrodes such that we could program an individual just as we now program a computer. It seems that the potentialities of computers are almost inconceivable as long as the programmer is able to live up to the capabilities of the machine. What about the possibilities, both good and bad, of a well educated or well "programmed" human mind?

P.L.C.

The editors would like to thank Dr. Jasper for his excellent editorial and the other contributors for their dedicated work in preparing this issue.

P.L.C. P.N.M.

Guest Editorial



HERBERT H. JASPER

Professor Jasper was born in the State of Oregon, United States (1906) and received his undergraduate education at Reed College, majoring in psychology and philosophy. Postgraduate studies in psychology were contined for a Ph.D. degree at the University of Iowa. He was then appointed Foreign Research Fellow of the Rockefeller Foundation for two years' study at the Sorbonne in Paris. At the end of this period he received the degree of Doctorat es Science (de l'Etat). His second thesis at this time was on the "electroencephalogram", a subject with which he became increasingly concerned for the next 25 years of his career. He was then appointed to the staff of Brown University in Providence, Rhode Island, and organized a laboratory of neurophysiology. In this laboratory the pioneer studies on the electrical activity of the brain were begun. In 1938 he was asked to join with Dr. Wilder Penfield in the work of the Montreal Neurological Institute on brain research. Recently Dr. Jasper was appointed first Executive Secretary of the International Brain Research Organization and Program Specialist in Brain Research in the Department of Natural Science of UNESCO. Dr. Jasper was co-author with Dr. Wilder Penfield, of the book "Epilepsy and Functional Anatomy of the Human Brain" and author or co-author of about 170 other publications in various scientific journals. He is undoubtedly one of the best known and most widely respected scientists in the field of neurophysiology.

Neurophysiology In Medicine

I am pleased and honored to have this opportunity to make a small contribution to the splendid work being done by the Medical Society of the University of Toronto, and particularly by your editors in the publication of this journal. The recent Student Research features are particularly outstanding, especially as they demonstrate the growing importance being placed upon research by medical students during the the course of their undergraduate training.

This is important not only for the relatively few who will choose to make a career of medical research, but because scientific methods of study, the humble critical enquiring attitude, the dissatisfaction with the limits of present knowledge, the doubts about didactic dogma, the inherent value placed upon new discovery and better understanding as opposed to personal profit or immediate practical application, and the rigid requirements of intellectual honesty in good research, may be more important than the body of medical knowledge acquired, knowledge which must be revised continually after graduation.

Neurophysiology has been considered, until relatively recent years, to be a highly specialized subject of largely academic interest, and of little practical importance in medicine. Even in clinical neurology and psychiatry, where it might be expected to play a most significant role, much of the research in experimental laboratories has been hard to relate to practical problems of the diagnosis and treatment of diseases of the nervous system.

This situation improved somewhat about 30 years ago with the development of electroencephalography. This technique was introduced by a psychiatrist, the late Professor Hans Berger of Jena, Germany, who recognized its great potential importance not only for neurology and psychiatry, but also for our understanding brain function in the intact unanaesthetized organism. For the first time, both in man and in experimental animals, it was possible to obtain objective records of the electrical activity of the brain during normal states of sleep, waking, emotional excitement, response to sensory stimulation, during motor activities, and even during the learning process. It was soon found that dramatic changes occurred in the E.E.G. during epileptic seizures, and that the form and location of these changes served as a sound basis for the diagnosis of different types of seizures. With electrodes placed directly upon the exposed cortex at operation the E.E.G. (or electrocortigram) served as a reliable guide to surgical excision of epileptogenic lesions. Characteristic changes were established for different forms and locations of brain tumours or abscess, for infections or metabolic diseases affecting the brain, either directly as in encephalitis, or indirectly as in hepatic coma, or pancreatic adenoma. It became possible to monitor the depth of anaesthesia, and the state of the brain during cardiac surgery.

As important as were these clinical applications, applications to psychiatry were disappointing. Further progress was limited due to lack of understanding of how the waves of the E.E.G. were generated. Their true functional significance in terms of activity within individual cells, synapses, and circuits within the brain was uncertain. Obviously there was need for more highly sophisticated studies of individual brain cells, their dendritic processes, the nature of their relationship with each other in synaptic nets and the role of the glia cells in which they are enveloped. We need to know also the chemical structure and metabolism of nerve and glia cells, and the chemical substances which transmit information from one cell to another, and the "hormonal like" substances which regulate their excitability.

During recent years neurophysiology has shared, to some extent, in the revolutionary explosion of knowledge which has characterized biomedical sciences in general. The electron microscope has revealed a whole new universe of ultra microscopic structure measured in angstroms (10^{-7} mm.) instead of micra (10^{-3} mm.). A new class of nerve fibres, measuring less than 0.5 micra was discovered, with physiological properties which may alter considerably our interpretation of the electrical activity of the brain. Several different forms of synapses have been shown to terminate on a single nerve cell with its dendrites, each with probably different chemical mediators stored in vesicles of different size and shape in the axonal terminals.

With intracellular or extracellular microelectrodes it is possible to record directly the membrane potential and to see the effect of the hundreds of synaptic events which may impinge upon a single cell.

With multibarelled micropipettes, minute amounts of chemical substances may be deposited by electrophoresis around a single nerve cell while recording its electrical activity.

By means of radioautographic and histochemical electron microscopy we shall soon be able to locate transmitter substance and their enzymes to specific sites on the cell membrane, or within intracellular organelles.

But with all of this ultramicroscopic information of single cells, how are we to reconstruct the systems of billions of cells in the functioning brain? How does it enable us to perceive a simple sensation, or not to perceive it when our attention is directed to something else, or when asleep? Where and in what form is sensory information coded and stored for recall in memory? How are perceptual experiences so altered by such drugs as LSD, or amnesia produced by scopolamine? Only very recently have such problems become reasonable problems for neurophysiological study, though their solution may be long in forthcoming.

GUEST EDITORIAL

Microelectrode studies of the firing patterns of individual brain cells are now possible in the human brain, even in subcortical structures during stereotaxic surgery with the patient fully awake. The surgeon (as well as the patient) may listen to coded information being transmitted by different cell assemblies, and be guided by their sound in the loud speaker for his surgical procedure. Many cells are encountered whose language is far too complex for decoding procedures as yet available, though each group of cells appears to have a highly specific function in the complex machinery of the brain.

It is obvious that the only possible solution to the more complex problems involving large systems of neurones, once their individual properties are more fully understood, is to be sought by the use of properly programmed computers. I am told by my colleagues at the Massachusetts Institute of Technology that there are presently more computer mathematicians at work on the brain than there are neurophysiologists. Computer analysis of neurophysiological data is becoming an essential part of both experimental and clinical neurophysiology today. Computer stimulation of brain function may become the only means of unravelling its complexities in the future.

With these and many other advances in technology and understanding, the gap between experimental and clinical nerophysiology should become steadily smaller. It will require close cooperation between clinical and laboratory workers if patients with nervous and mental diseases are to benefit from the many and varied advances being made in experimental neurophysiology today, and in the years to come.

It will require, as well, a joint effort with anatomists, neurochemists, neuropharmacologists, neuroimmunologists, biophysicists, molecular biologists and others if we are to make significant major progress in this field. With this in mind an International Brain Research Organization (IBRO) has been formed, incorporated in Canada, working jointly with UNESCO in Paris, to promote the basic science of the brain.

With over half our hospital beds filled with neuro-psychiatric patients, and many others in which the nervous system is importantly involved, the challenge for research in the neurosciences is very great indeed. After forty years of work in this field, I can assure you that the road ahead is rough and devious but very rewarding.

HERBERT H. JASPER, F.R.S.C.
Professor of Neurophysiology,
University of Montreal

Aspects Of Peripheral And Spinal Mechanisms In Cutaneous Sensation

T. Picton 6T7

The understanding of cutaneous sensory mechanisms has recently been a source of rather heated controversy. This paper will attempt to touch upon some of the modern theories of how one is conscious of the modality and intensity of a cutaneous stimulus. It limits itself to the more simple mechanisms of the peripheral receptor and the spinal cord; yet from an understanding of these mechanisms perhaps some insight into the nature of perception may be obtained.

I CHANGING CONCEPTS OF CUTANEOUS SENSATION[1 6 8]

Physiology follows physics. Physics provides the tools with which the physiologists conduct their experiments; it also provides the models for physiological analogies. Thus explanations of perception have varied according to the physics of their age: nineteenth century concepts followed the definiteness of cause and effect, whereas modern sensory concepts are permeated with ideas from current information theory—pattern, coding, probability.

In the early part of the last century Müller proposed his doctrine of specific nerve energies: the sensation caused by stimulation of a sense organ is always specific for that sensory system (when the retinal nerve endings are discharged either by light or by mechanical trauma one always experiences the sensation of vision.) Later von Frey separated Müller's sense of touch into the classical four modalities of pressure, heat, cold and pain; to each modality he assigned a specific sensory receptor. It took little time to demonstrate the folly of this correlation of modality to specific anatomic receptors[8]; recently Weddell administered the coup de grâce to this concept by demonstrating that the free nerve endings of the cornea (which lacks anatomically specialized endings) could differentiate between all four modalities.[2] These specificity theories seem based on a "linear" concept of nervous action: a sensory stimulus activates a specific sensory receptor whose discharge is transmitted along a direct pathway to be received in a precise cortical sensory area.

The great interaction of all parts of the nervous system, however, makes its action three-dimensional rather than linear. Thus in the 1950's Weddell[2,4] proposed a pattern theory of cutaneous sensation: a stimulus applied to an area of skin causes not the activation of specific receptors in that area but the firing, in varying degrees, of all the receptors in the region; a decodable pattern results from this total receptor discharge. Different sensory modalities result therefore from different discharge patterns in the same fibre bundle rather than from a selective activation of a few fibres in that bundle (figure 1). Yet pattern theory is not a complete disavowal of specificity. Without at least some degree of specificity it is impossible to transmit information—one may as well attempt to understand a pattern woven in threads of the same colour. Melzack and Wall[8] present a concept of sensation as a pattern of impulses mediated by the specialized component parts of the nervous system. Every sensory receptor has its own distinct response profile reacting to many stimuli but more easily to certain of them; the frequency of discharge varies with the intensity of stimulation but the receptors have thresholds to all types of stimuli. The decoding of sensory pattern therefore requires the analysis of the frequencies of many fibres (figure 1).

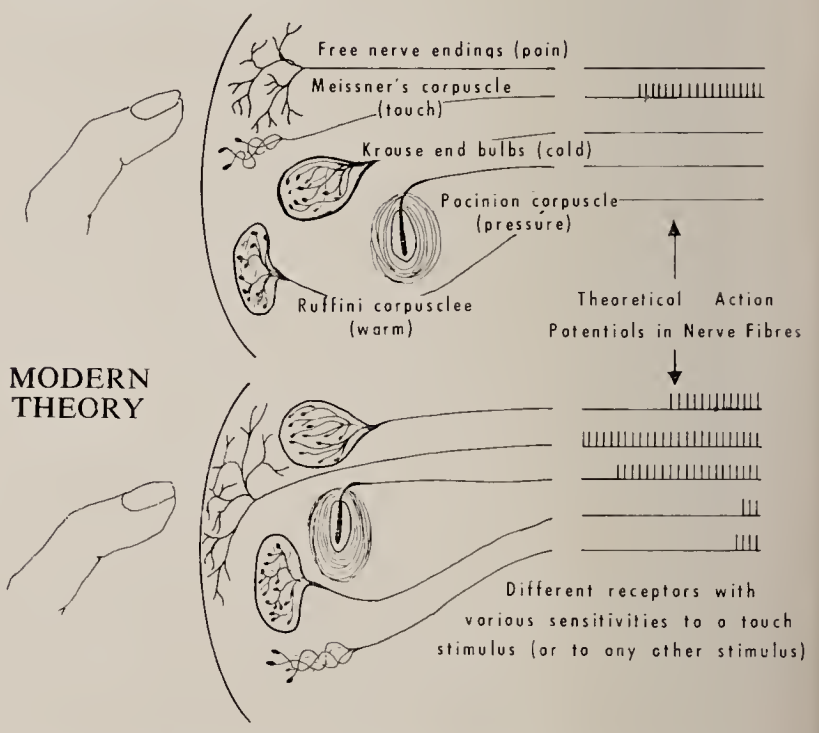
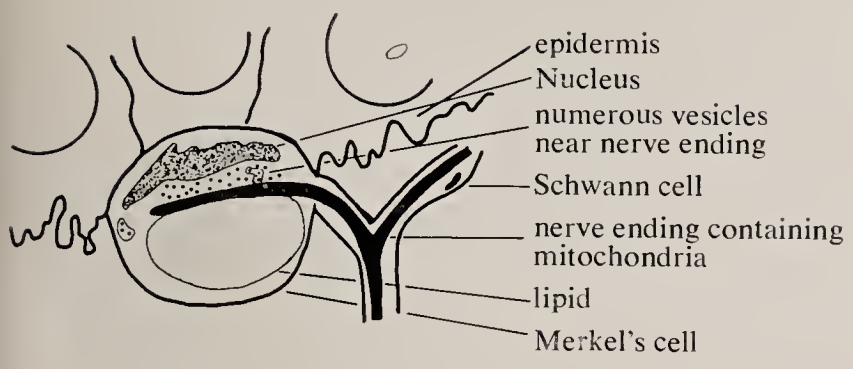

CLASSICAL THEORY
Free nerve endings (pain)
Meissner's corpuscle (touch)
Krause end bulbs (cold)
Pacinian corpuscle (pressure)
Ruffini corpuscles (warm)
Theoretical Action Potentials in Nerve Fibres
MODERN THEORY
Different receptors with various sensitivities to a touch stimulus (or to any other stimulus)

FIG. 1: Diagram representing the *specific nerve terminals* of classical theory and *the patterns of activity in groups of receptors* of modern theory.

II THE PERIPHERAL SENSORY RECEPTOR

anatomy—see figure 2 and table 1

modern concepts of specificity—It is strange that Sherrington's description of specificity in 1900 is quite in keeping with modern sensory theory: "The sensorial end-organ is an apparatus by which an afferent nerve fibre is rendered distinctly amenable to some particular physical agent and at the same time rendered less amenable to, i.e. shielded from, other excitants."[8] There is evidence now that certain receptors may respond to



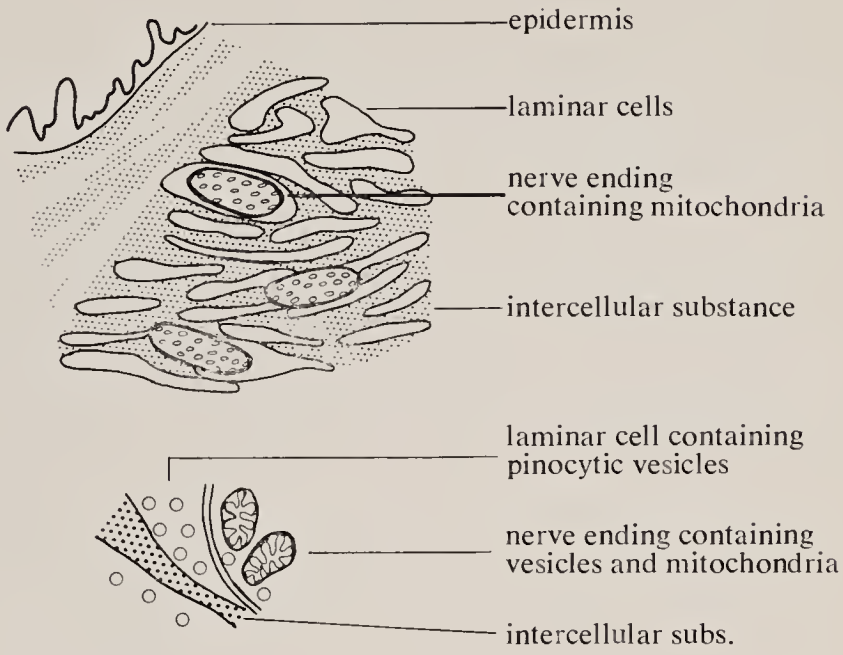


FIG. 2: Diagrams representing the electron microscopic structure of two types of sensory nerve terminals[5]—notice the presence of possible transduction cells and the many vesicles in these cells and the nerve ending; left figure represents a Merkel's disc and right figure a Meissner's corpuscle (with area of greater magnification below).

stimuli of more than one modality. Hunt and McIntyre[13] have demonstrated receptors in the cat that respond to touch with a high frequency discharge and to heat with impulses of a much slower frequency. On the other hand Iggo[2] has demonstrated that some mechanoreceptors were excited by a fall in skin temperature (thereby explaining Weber's illusion that weights feel heavier when cold.) Yet some sensory receptors seem to be more specific than was previously thought—some thermoreceptors as well as responding to a positive or negative temperature change also have a peak sensitivity in a certain temperature range.[8] Melzack and Wall[8] therefore propose a response profile of cutaneous sensory receptors based upon six physiological properties:

—threshold to mechanical distortion
—threshold to positive or negative temperature change
—peak temperature range sensitivity
—threshold to chemical change
—stimulus strength response curve
—rate of adaptation.

Thus the different responses of various receptors (which together form a pattern of nervous activity) will delineate how well the stimulus fits into the response profiles of the individual end-organ. Each receptor responds to its highest degree at a definite point in a "multi-dimensional space of physiological variables"[8]— a certain receptor, for example, may respond most to a very warm, slightly painful, light tactile stimulus. Localization of a stimulus in this continuum of sensory characteristics requires the comparison of the responses of several receptors.

transduction mechanisms — The role of chemicals has been studied extensively as transducers of the sensations of pain and itch. Pain may be produced experimentally by potassium, acetylcholine, serotonin and histamine. Recent evidence of Keele[5] seems to implicate a "pain producing substance" similar to bradykinin as the ultimate chemical transducer of pain (possibly released or activated by the other substances). The bradykinin concentration of synovial fluid during an attack of gout is greatly elevated—urates may themselves cause kininogen activation by physical means or may release kininogen-activating enzymes from lysosomes. The two substances implicated in the sensation of itch are histamine and the proteases. "Prickly heat", possibly the most severely pruritic of human ailments, is caused by the retention of sweat in the epidermis—sweat gland secretions have a very high protease concentration.

Mountcastle[5] suggests the possibility that all nerve endings are chemoreceptors. Indeed, large number of vesicles and granules probably containing specific chemicals are shown by electron microscopy in the nerve endings and associated cells. (Figure 2)[4,5] This is not a new proposition—Merkel in 1880 suggested that sensory nerve endings are activated by chemicals released on stimulation of "Tastzellen" or transducer cells. In the free nerve endings chemical changes in the extracellular fluid may be the activating mechanism rather than the specific release of chemicals at the nerve ending. Loewenstein[5,14] maintains, nonetheless, that in the Pacinian corpuscle mechanical distortion of the nerve is the only event required for discharge.

Rushton[3] points out that in the simplest of animals sensation is basically the release of chemicals upon stimulation. These substances diffuse to other cells in the organism and initiate an appropriate response. With the increase in animal size and the differenitiation of cells into tissues, diffusion of chemicals alone became an inadequate means of effecting a response to a sensory stimulus. The evolution of nerves allows for the fast secretion of chemicals in a precise and distant location —thus effecting a more exact and immediate response to sensation. Thus sensation may be considered "the play of chemicals in a chemical playground".[3]

III THE DORSAL HORN CELL

convergence on the dorsal horn cell—referred pain[1]— There are many more fibres in the posterior nerve roots

TABLE 1 ANATOMY OF SENSORY NERVE ENDINGS

Nerve Ending	*Description*	*Location*	*Action*
free nerve endings	axons travel in groups within strands of Schwann cell cytoplasm at times approaching the surface of the cell to be bathed in extracellular fluid	dermis and epidermis of all skin areas	responds to all stimulus modalities
follicular nerve endings	basket-like network of free nerve endings surrounding hair follicles	hairy skin	probably rapidly adapting mechanoreceptors
Meissner's corpuscles (similar to those of Ruffini?)	tree-like endings intimately related to certain connective tissue (laminar) cells	the papillae of non-hairy skin	probably slowly adapting mechanoreceptors
Vater-Pacinian corpuscles (similar to Krause end bulbs and genital corpuscles?)	a single nerve fibre surrounded by concentric lamellae of flattened cells and collagen fibres	subcutaneous tissues	rapidly adapting mechanoreceptor
Merkel's disc	groups of nerve fibres in contact with "tactile cells"	the junction of the dermis and epidermis in hairless skin	probably a mechanoreceptor

than there are primary relay neurons (cells ascending to the thalamus from the dorsal horn or from the cuneate and gracilis nuclei). Therefore fibres carrying pain patterns from the skin and those from the viscera may well terminate upon the same set of relay neurons. Visceral pain may thus be transmitted to the brain along the same neurons as cutaneous pain—and may be perceived as coming from the skin (this is the convergence-projection theory of referred pain). Visceral pain impulses may facilitate normal cutaneous afferent impulses such as light touch so that discharge of the relay neuron reaches the intensity of a pain pattern (this is the convergence-facilitation theory of hyperalgesia).

substantia gelatinosa and the gateway theory of pain (figures 3 and 4)[12]— Melzack and Wall propose the substantia gelatinosa as a gate or trigger mechanism in the sensation of pain. Their basic concept is similar to that of Weddell[7]— pain is a pattern resulting from the summation of normal cutaneous afferents rather than from specific pain receptors. The firing of the dorsal horn cell in the transmission of pain depends upon two things: its stimulation by incoming sensory fibres and its inhibition by the cells of the substantia gelatinosa. It is suggested that the larger afferent fibres excite the gelatinosa cells (therefore decreasing their own effect on the dorsal horn cells) whereas the unmyelinated fibres inhibit them.

The elegance of this theory rests upon how well it explains the known facts about pain. Psychological studies and experiments using local anesthetics seem to show two different pain sensations: an immediate short sharp sensation and a burning sensation of later onset and longer duration.[1] This could easily result from the different transmission speeds of the larger and the smaller cutaneous fibres. Incomplete damage to a nerve root or a peripheral nerve has its main effect on the larger myelinated fibres of that nerve—and the subsequent release of the dorsal horn cell from gelatinosal inhibition results in causalgia (constant) or neuralgia (episodic). A similar mechanism may be operating during the lancinating pains of tabes dorsalis (which involves degenerative changes in the posterior nerve roots as well as the posterior columns). When leprosy[7] affects the nervous system the patient is unable to fell pinprick (insufficient nerve fibres active to convey slight pain) but when pinched he experiences an excruciating pain (relatively decreased action of the larger fibres). Pain is often relieved by gentle massage or heat—both of which may activate the larger nerve fibres resulting in closure of the gelatinosal gate. In a similar way phantom limb pain may be relieved by tapping the stump gently with a rubber hammer. Vibration summates with highly painful stimuli (due to direct effect on the dorsal horn cell and inability to overcome the inhibition of the substantia gelatinosa) but relieves low pain sensation (by activating the substantia gelatinosa).

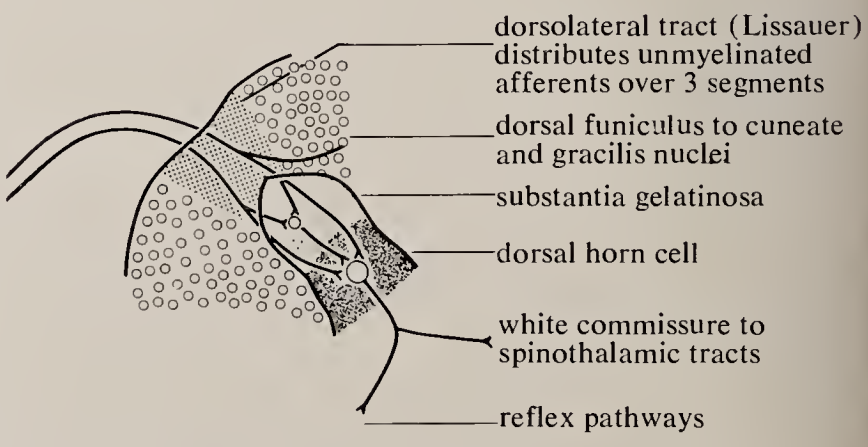

dorsolateral tract (Lissauer) distributes unmyelinated afferents over 3 segments
dorsal funiculus to cuneate and gracilis nuclei
substantia gelatinosa
dorsal horn cell
white commissure to spinothalamic tracts
reflex pathways

FIG. 3: Diagram representing the anatomy of the dorsal horn.

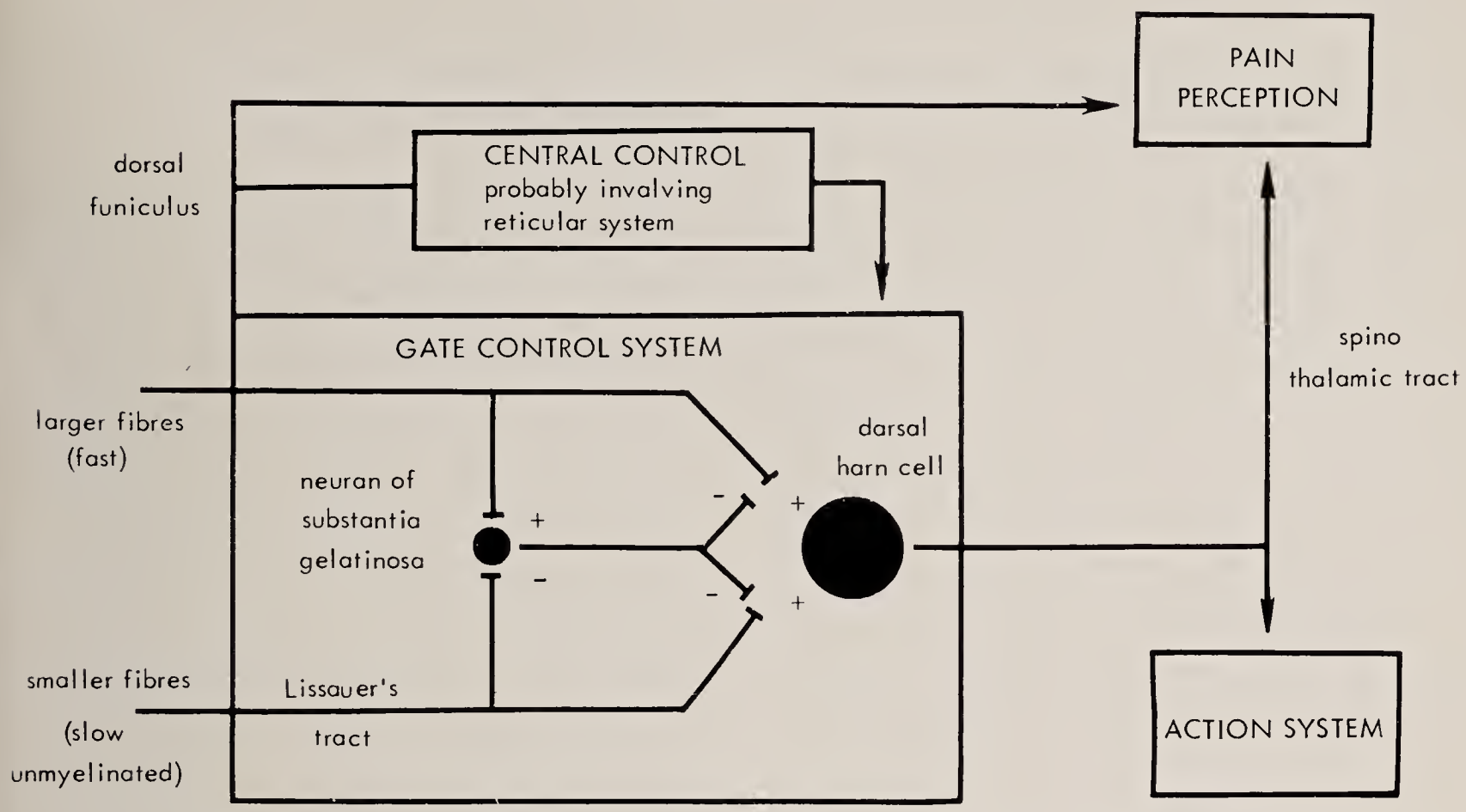


FIG. 4: Diagram showing the mechanisms of the gateway theory of pain — modified from Melzack and Wall[12].

As can readily be seen there is a basic division between the modern theories of pain sensation. One theory stresses the action of various chemicals upon the peripheral nerve endings; in the other the sensation of pain depends upon the effect of different fibres on the cells of the dorsal horn. One would think that post-mortem examination of patients with the clinical syndrome of pain insensitivity would solve this dilemma. Unfortunately the pathological picture is far from clear.[10] Indeed one patient showed an absence of free nerve endings[10] whereas another lacked the smaller fibres in the dorsal roots and possessed no tract of Lissauer.[9]

relay networks—The output from a synapse is dependent upon but not equal to its input. Fessard[3] demonstrates that by virtue of anatomical structure (into networks) a synapse may demonsrate such processes as amplification and tuning (figure 5). These various synaptic actions have been used to explain the controversial subject of itch sensation. Itch has a great similarity to pain: as in pain the free nerve endings and the unmyelinated nerve fibres seem to be necessary for its sensation. Itch seems to be brought on by a stimulus which, if it were more intense, might result in pain: a light touch by a needle tickles; injection of histamine at a certain concentration results in a sensation of itch but at twice this concentration pain results. Yet itch is a distinctly different psychological sensation from pain. Wall[3] suggests a theory that increasing cutaneous input will at first result in a slow increase in the output of the dorsal horn cells; further increase may result in feedback and an alternating pattern of horn cell discharge; even greater input will cause an overriding of inhibitory feedback and a constant discharge pattern. Possibly an alternating pattern may be the physiological representation of itch, and a constant pattern that of pain. As in the sensation of pain there is controversy over the relative roles of the peripheral receptors and the relay neurons.

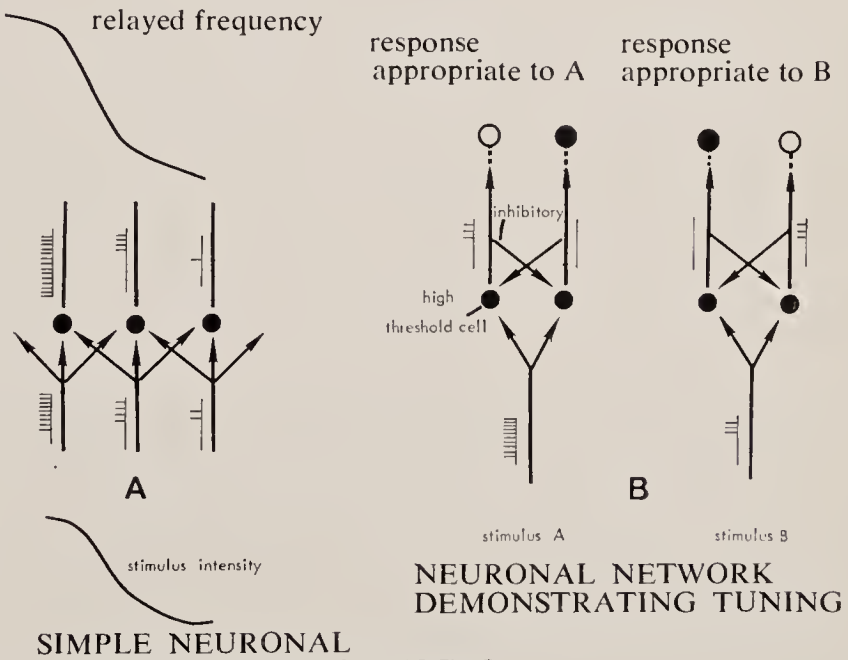


FIG. 5: Diagram showing theoretical neuronal networks that evidence suggests may be operating at dorsal horn level — modified from Fessard[3].

IV SPINAL SENSORY PATHWAYS

dual sensory pathways—There are two separate pathways for sensory information to travel to the brain: the crossed spinothalamic tracts and the uncrossed dorsal columns. Classical theory postulates that each tract mediates different types of sensory information (table 2). Indeed on the basis of this duality Head proposed a classification of sensation into the protopathic and the epicritic, the protopathic being a primitive and generalized system mediated by the spinothalamic tracts, and the epicritic a more advanced and specific system involving the dorsal columns. Recently, however, much doubt has been cast upon this absolute dichotomy. Spinothalamic tractotomy does not always relieve pain; electrical stimulation of the dorsal columns may result in pain sensation; two point discrimination is never permanently lost after surgical section of the dorsal columns. It may be suggested then that the dichotomy is not complete; patterns of pain and temperature sensation though usually transmitted by the spinothalamic tracts may if necescary utilize the dorsal columns. The fewer the transmission lines, however, the harder it is to send a patterned message.

TABLE 2 SPINAL SENSORY PATHWAYS

locus of sensation	*posterior columns*	*spinothalamic tracts*
cutaneous sensations	touch pressure	
	localization	pain
	two point discrimination	warmth
	stereognosis	cold
	vibration	sexual sensations itch and tickle
muscle and joint sensations visceral sensations	proprioception kinesthesia	muscle fatique muscle pain
		visceral pain bladder fulness, etc.

wet and dry—These are complicated sensations. They are closely related to cold and hot sensations but also involve touch receptors; it can therefore be assumed that their representative patterns are more complicated than those of the temperature senses, and their transmission more easily interfered with. Nathanson[11] points out that minimal damage to the spinothalamic tracts that cannot be detected by the usual tests for sensation may be demonstrated by the patient's inability to discriminate between wet and dry. Examining the sensations of soft and hard or rough and smooth may also be used to demonstrate minimal dysfunction of the sensory neuronal network.

V THE HOMUNUCULUS AND PERCEPTION

Various details in the peripheral and spinal mechanisms of sensation have been collected into this paper. The complicated nature of these simple mechanisms serves only to suggest the extreme intricacy of the complete sensory response. Yet in all of this where resides that process called "perception"? Attneave[3] points out that most theories of sensation seem to take for granted the presence of a perceiver, "a homunculus who has some awareness of the outside world as a result of sensory data received and directs the organism accordingly." In modern science the very mention of a perceiver, however, conjures up "visions of a fluffy cloud of non-matter hovering in the pineal region (perhaps connected to that body by a slender strand of ectoplasm), resistant to extirpation, insensitive to microelectrode stimulation and generally quite beyond the pale of scientific investigation." Bullock[3] attributes neuronal rather than metaphysical qualities to this homunculus; he describes the properties of theoretical cells or groups of cells that recognize incoming sensory patterns and trigger appropriate responses. Attneave suggests that these "decision cells" form what is known as the reticular system. Yet in reality our knowledge of "perception" or "awareness" is minimal—all we know is that awareness resides somewhere in the ever-changing pattern of impulses that travels the intricate network of our nervous system.

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Student Research

Sensory Deprivation And Mental Illness

Western literature and popular thought have long been fascinated by the relationship between isolation and madness. The belief in such a relationship has been fostered by explorers, prisoners in solitary confinement, mystics and others exposed to isolation, whose observations have drawn attention to the effects on human behaviour of decreased environmental stimulation.[1]

When D. O. Hebb began studying the effects of sensory deprivation at McGill in 1951, he was preoccupied by the defection of large numbers of American soldiers to China during the Korean War. Hoping to gain an understanding of the process of brainwashing, he began to test the effects of isolation. Hebb's pioneer experiments demonstrated that sensory deprivation could lead to psychotic behaviour. Since then, the notion that sensory deprivation is an important factor in the causation of mental illness has been increasingly supported. Its developmental importance has also been stressed; a number of investigators have shown that deprivation early in life of the organism creates permanent difficulties in adaptation to adult life.[7] The implication is that psychological development is dependent on stimulation from the environment.

Sensory deprivation has served as an explanatory model for paranoid psychoses which frequently develop among prisoners in solitary confinement. The transient psychoses frequently observed in medical and surgical situations in which the patient is immobilized, isolated and subjected to definite limitations of sensory input have been explained in terms of sensory deprivation rather than by previously preferred "toxic" theories.[10] One sueh deprivation situation is that of cataract extraction followed by bilateral eye patching.[3] A positive correlation has also been established between deafness and a higher incidence of psychosis.[6]

Other implications of sensory deprivation are evident as well. For example, it has been suspected that sensory deprivation in aviation plays a part in reducing the efficiency of some pilots, leading to otherwise unexplained confusion in flight.[2]

THE CLASSICAL EXPERIMENTS

Hebb's associates, Heron, Baxton and Scott, explored the effect on human volunteers of the deprivation of light, sound and tactile stimulation.[5] After several days of sensory deprivation, 25 of 29 subjects reported hallucinations, defined as "perceptions without object". These experiences were most commonly visual, and typically progressed from the simple to the complex. Lines or dots of light would appear, followed by geometrical patterns, isolated objects, and finally full-blown scenes which seemed to be in front of the subjects. They were often so vivid as to prevent the subject from sleeping. In addition to the hallucinations, a wide variety of behavioral and subjective effects were reported. These included depersonalization, somatic delusions, disorientation in time and space, and deterioration in the ability to think and reason.

As systematic investigation of these phenomena became more widespread, experiments fell into three groups:

(i) *absolute* reduction of sensory stimulation (*e.g.*, darkness, silence, immobilization of joints);

(ii) reduced *patterning* of sensory input (*e.g.*, masking sounds, ground-glass goggles, cardboard gloves and cuffs to decrease tacile and kinesthetic stimuli);

(iii) imposed *monotony* of sensory environment (*e.g.*, a small, unchanging visual field).

HALLUCINATIONS

Reports of hallucinations in sensory restriction research were reviewed by Zuckerman and Cohen, who divided the reported visual and auditory sensations into two categories.[16] The *meaningless* sensations were described as flashed of light, spots, and simple noise. This category included "simple idioretinal responses or illusions". The *meaningful* sensations, on the other hand, signified greater cortical involvement. These true hallucinations involved people, objects, complex scenes, or sounds of voices or music.

The exclusion of relatively simple perceptions from the category of true hallucinations was supported by other investigators, who found that various hallucinations, generally considered to be manifestations of psychosis, were quite common under normal sensory conditions. Subjects exposed to 10-30 minutes of darkness or just lying quietly in a room with no restrictions of sensory input have frequently reported hallucinatory experiences of varying degrees of complexity.[16] The hallucinations, however, often disturbing to the subjects associated with psychotic behaviour, have dramatically suggested the possible parallel to clinical psychoses and to certain drug reactions..

MECHANISMS

Various theories have been advanced to explain the results of sensory deprivation. Most have been in psychological or psychiatric rather than in neurophysiological terms. Thus Werner[7] suggests that the results represent a regression to an archaic form of sensory experience, in which objective and subjective perceptions are not yet

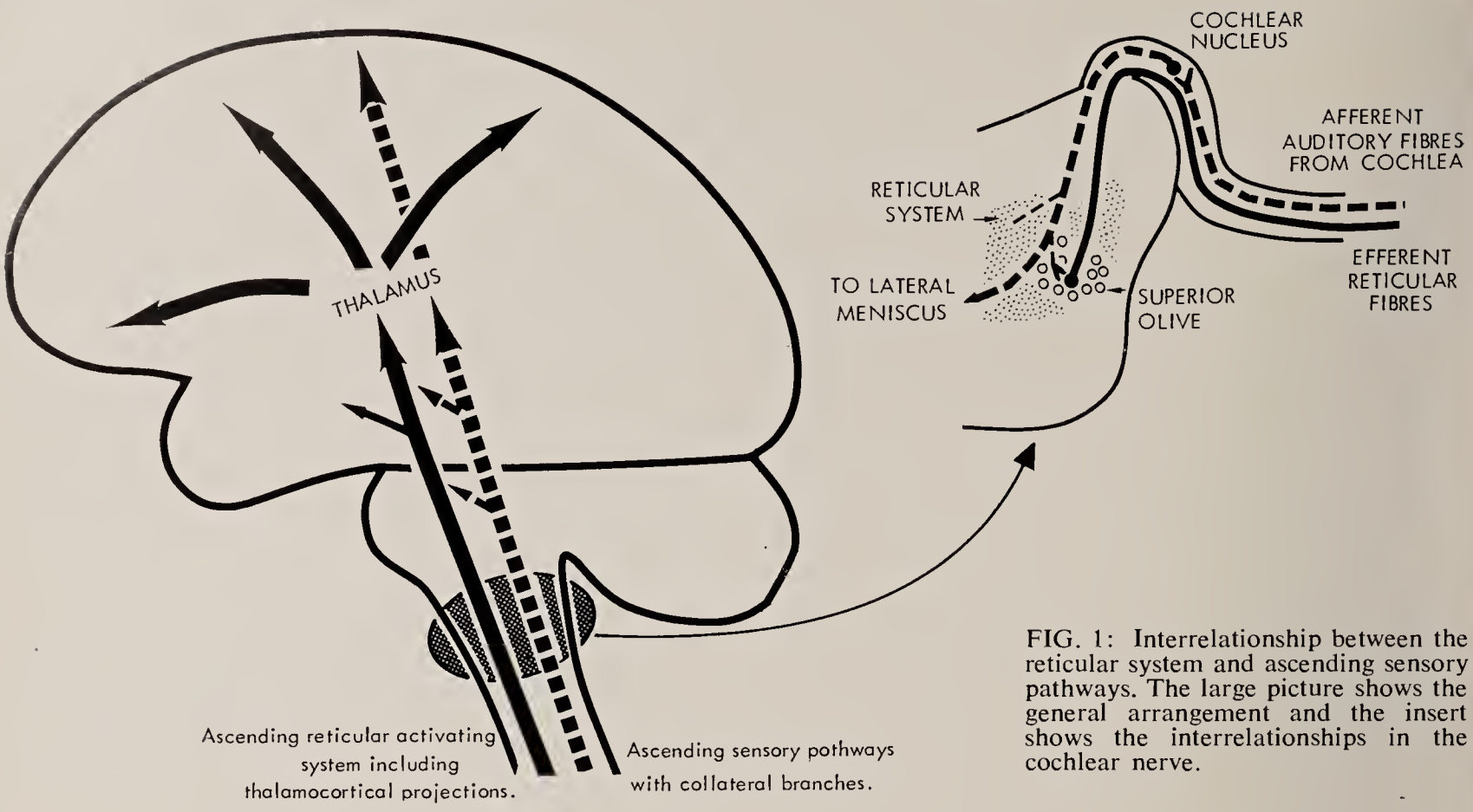

FIG. 1: Interrelationship between the reticular system and ascending sensory pathways. The large picture shows the general arrangement and the insert shows the interrelationships in the cochlear nerve.

differentiated. Rapaport[7] views sensory deprivation as a state in which there is a disruption of the relative autonomy of the ego-functioning with respect to the id and the environment. In the absence of external stimulation, normal reality contact is interefered with, the ego cannot maintain its autonomy, and the id brings up hitherto unconscious material. The characteristics of the primary process can be seen in the effect, imagery (hallucinations), and in the changes of perceptual and cognitive abilities.

RETICULAR ACTIVATING SYSTEM

The possible role of the ascending reticular activating system (ARAS) in behaviour observed during sensory deprivation is suggested by its role in attention and alerting, and by its diffuse nature. Located in the midbrain reticular formation in the core of the brain stem, its axons have been traced into virtually every identifiable nuclear area within the central nervous system.[15] They have also been traced via diffuse thalamocortical projections to virtually all areas of the cerebral cortex.

The ARAS parallels the classical sensory pathways (fig. 1). Its central location permits it to sample incoming stimuli via collateral branches of these afferent tracts. Thus a sensory stimulus of any modality may stimulate the ARAS, which in turn activates the cortex to produce general alerting and arousal.

Lindsley[8] proposes that in monitoring sensory inflow, the ARAS becomes adjusted to certain levels of activity. If one restricts the sensory input to the ARAS, it can adjust to the change only within limits. If the sensory restriction is more persistent or more marked, it may lead to new modes of response of the ARAS which are projected upon the cortex. Thus attention, perception and emotion are influenced, accounting for the phenomena observed in sensory deprivation.

RETICULAR CONTROL OF SENSORY INPUT

In addition to causing arousal, the reticular formation also acts as a central regulator of sensory input. This feedback control over different sources has been demonstrated for every one of the sense modalities. The effect is exerted at the first central relay in each of the major pathways, and in some cases (audition and proprioception) extends as far peripherally as the sense receptor itself.[9]

For example, a bundle of efferent fibres travels with the eighth cranial nerve from the region of the superior olive to the contralateral cochlea, and it has been shown that stimulation of the medulla in certain areas will cause suppression of auditory nerve responses to a standard stimulus.[1]

The regulation is almost always inhibitory, and probably serves to exclude irrelevant sensory information during the focussing of attention. Hernandez-Peon, Scherrer and Jouvet have recorded the response of the cat's cochlear nucleus to serially repeated click stimuli. They found that the prominent potentials produced by the clicks in the relaxed or drowsing state were markedly diminished when the animal's attention was attracted by visual or olfactory stimulation[9] (Fig. 2).

Further evidence for the inhibition of sensory input came from the discovery that stimulation within the

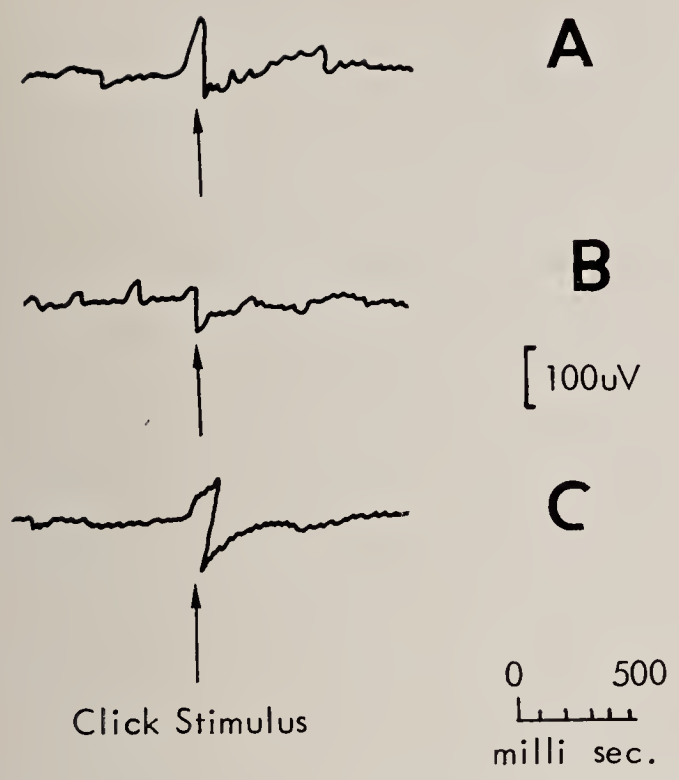

FIG. 2: Ink written records of response of cochlear nucleus of cat to click stimulus. A—Cat inattentive, "relaxed"; B—Cat attentive to visual stimulation, "alert"; C—Cat inattentive again (Magoun).

brainstem's reticular core blocks the post-synaptic component of an afferent volley from the dorsal spinal roots. Through this inhibition, the reticular formation normally prevents many impulses from reaching the levels in the brain at which they are normally perceived. Pos at the University of Toronto suggests that disturbances in this sensory input-regulating system may lead to sensory deprivation, or, as he calls it, informational underload of the brain.

SENSORY DEPRIVATION AND MENTAL ILLNESS

Hallucinations are a common symptom in many mental illnesses (*e.g.*, organic psychoses, schizophrenia) and in several experimental conditions such as sensory deprivation and drug-induced psychoses (*e.g.*, LSD-25, mescaline). The fact that some drugs, such as chlorpromazine, tend to abolish these hallucinatory states suggests that these states may have, in spite of their differences, a neurophysiological mechanism in common. Pos[12, 14] suggests that this common factor may be the state of informational underload of the brain. According to this hypothesis, the brain for its normal awake functioning is dependent not only on stored intracerebral information, but also on a certain level of extracerebral input. When this input drops below a certain threshold, the brain is believed to be in a state of informational underload which can be identified physiologically.

The state of informational underload may thus be the common factor responsible for the hallucinations of sensory deprivation, psychotic mental illness, and LSD and mescaline reactions. The "hallucinations" of dreaming (which has been called "physiological insanity") may be caused by the same mechanism.

A significant question arises at this point: can interference with the sensory input-regulating system occur, resulting in increased or decreased filtering of sensory input? If so, a neurophysiological model of psychosis emerges. According to this model, a variety of pathogenic factors in psychosis (genetic, toxic-metabolic, degenerative, faulty learning, etc.) may influence the sensory input-regulating system to cause informational underload.

THE POS RESEARCH[13]

Investigating the sensory deprivation hypothesis of mental illness is a formidable task, likely to occupy many researchers for many years. The first step is to determine whether in fact there is a neurophysiologically definable syndrome of sensory underload. Using cats in a specially designed box, Pos varies auditory, visual and proprioceptive stimulation (the latter by means of succinyl choline-induced muscle paralysis) singly and in different combinations. In the pilot phase of the experiments, electrodes are arbitrarily placed, one on the frontal, one on the parietal, and one on the occipital cortex of each side. Electrical activity is recorded under experimental conditions of absolute reduction, reduced patterning, and imposed monotony (white noise) of sensory stimulation.

The EEG tracings are analyzed by computer for regularly occurring activity; in essence, the computer emphasizes the regular at the expense of the irregular components at each frequency. The computer also establishes the difference in phase between the electrodes. The EEG tracings have been converted into autocorrelograms and autospectrograms.

By this method, Pos has studied the electric activity of the six brain areas for a period of 250 milliseconds following presentation of a light stimulus to the animal every 60 seconds. The computer averages immediately the 60 consecutive responses. The cortical responses evoked by regular light flashes at the end of a sensory deprivation experiment indicate a considerable change in the reactivity of the cortex-as-a-whole as compared to the responses evoked before an experiment starts. The spectrum of rhythms occurring in different brain areas narrows, in that fewer rhythms occur and the centre of this activity shifts to the lower frequency range of the spectrum.

This change occurs when the animal is subjected to white noise and it is exaggerated when the white noise is combined with darkness. The next step in the approach which stresses spatial interrelationships in the brain is further mathematical analysis to estimate the degree of interdependence betwen the various EEG traces.

This study of the relationships between the different brain areas stresses the function of the brain as an integrated whole, an approach which is felt to be more

applicable to the investigation of mental illness than the study of one particular area or structure.

THE FUTURE OF RESEARCH IN SENSORY DEPRIVATION

Much remains to be done. Future studies will have to involve control studies with other species, to avoid preoccupation with what might be species-specific phenomena. It will be necessary to compare the results from superficial electrodes with those from electrodes placed deep in the brain. It will also be of interest to learn if the neurophysiological syndrome can be brought about in other ways, such as by psychotomimetic drugs, diffuse brain damage, conditioning, overwhelming anxiety, dreaming, etc.

Thus current research in neurophysiology is attempting to answer questions that have been raised by discoveries in sensory deprivation. The result may be new and important knowledge about mental illness.

P. Newman, 6T8

ACKNOWLEDGEMENT

My sincere thanks to Dr. R. Pos, Department of Psychiatry, Toronto General Hospital for his assistance in the preparation of this article.

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The Action Of Drugs On The Cell Membrane

I. Laufer 6T7

1. INTRODUCTION

Most drugs must encounter the surface of several different cells before reaching their target site. These cells include those lining the gastrointestinal and respiratory tract, skin and blood vessel in addition to the cells of the target organ. To most drugs these membranes act only as *passive diffusion* barriers governing the concentration of the drug within the volume enclosed by the membrane. Thus drugs with higher lipid solubility such as unionized acetylsalicylic acid are completely absorbed through the gastrointestinal tract, whereas polar molecules such as acetylcholine are poorly absorbed. The penetration of some drugs through membranes is *facilitated*, that is, the rate of diffusion is much faster than the rate calculated from the concentration gradient across the membrane. For example, glucose entry into red blood cells proceeds at five times the rate of passive diffusion, but the diffusion is still down the concentration gradient. There are some substances which cross membranes against electrical or chemical concentration gradients. This process requires the expenditure of energy, and is called *active transport*. In nervous tissue the active transport of Na^+ and K^+ may utilize up to 40% of the energy of the resting cell. Other examples of active transport are glucose and amino acid transport across intestinal and renal tubular cells, catecholamine transport at the post-synaptic membrane of the adrenergic synapse, and iodide transport into thyroid cells.

In addition there are certain classes of drugs for which the cell membrane acts neither as a diffusion barrier, nor as a mechanism to facilitate its entry into cells. For these drugs, *the membrane itself is the target organelle* and by causing physio-chemical changes in this membrane, these drugs produce their biological effect. These classes of drugs include local and general anaesthetics, psychotropics, neural transmitters (adrenergic and cholinergic), cardiac glycosides and mineralocorticoids. This paper will be limited to a general discussion of the effect of drugs on the cell (plasma) membrane with reference only to drugs whose primary effect is on the nervous tissue.

II. STRUCTURE OF THE CELL MEMBRANE

This has been the subject of many papers and reviews in recent years (Burgen, 1962; Finean, 1966; Green and Perdue, 1966; Kavanau, 1965, 1966; Ling, 1962, 1965; Robertson, 1962; Biochemical Society Symposium, 1962).

The concept of the cell membrane which is most widely held will be discussed briefly. Under the electron microscope, a typical membrane in an osmium tetroxide fixed preparation appears as two dark lines each approximately 20 Å thick enclosing a band of lighter staining material approximately 35 Å thick. The dark bands probably represent the osmiophilic polar end groups of phospholipids, whereas the light band represent the hydrocarbon chains of lipid molecules. The uniformity in the appearance of cellular membranes is emphasized by Robertson (1962). At the electron microscopic level there is no hint of variety in the chemical composition and function of different membranes from different tissues or even of different sections of a single membrane. The post-synaptic membrane of an axon is chemically excitable but electrically inexcitable, whereas the conducting portion is excitable only electrically. However no morphological differences have been demonstrated between these two parts of the axon. The contemporary molecular model of the cell membrane is still similar to that proposed by Danielli in 1935. The present model postulates basically a bimolecular leaflet of lipid sandwiched between two layers of protein. (Fig. 1)

The *lipid* phase consists of equal quantities of phospholipid and cholesterol in a highly hydrated layer. The phospholipid aggregate forms a film of bimolecular leaflets with their hydrocarbon groups apposed and their polar end groups entering the aqueous solution. The Van der Waals forces between adjacent hydrocarbons is the main force giving stability to the lipid phase. These forces are increased by cholesterol which causes a closer packing of the molecules. Some of the physical characteristics of the membrane, such as its refractive index, surface tension, capacitance, water and lipid permeability are due to this lipid double layer.

Protein is believed to be absorbed onto the polar end groups of the phospholipids. This protein is important in maintaining the structural integrity of the cell adding strength and elasticity to the membrane. In addition, this structural protein may have great influence on cell function. It may alter the structure of the lipid phase; it markedly lowers the surface tension of the lipid layer. Besides structural protein, the membrane contains enzymatic protein such as the Mg^{++}, Na^+, K^+—activated adenosine triphosphatase (ATPase), which is believed to play a role in active cation transport (Post *et al.*, 1960). Surface protein, either structural or enzymatic, may contain combining or active sites for drugs.

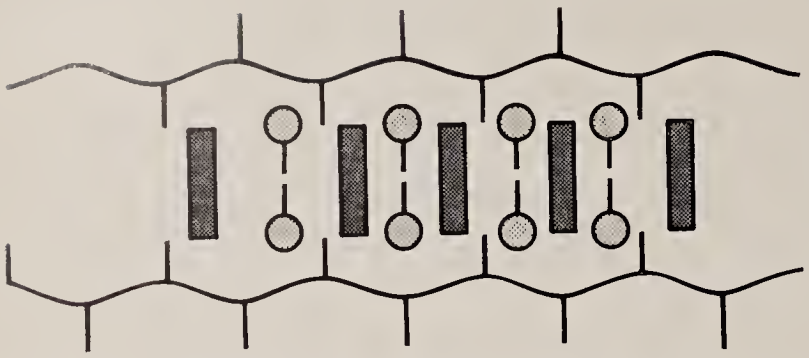

FIG. 1: Molecular model of cell membrane. The wavy line represents the polypeptide backbone of protein with protruding amino acid residues. The lightly shaded molecules are phospholipids with their polar and hydrocarbon ends. The more darkly shaded molecules are cholesterol.

Water comprises about 78% by weight of brain tissue, yet in the past very little attention was paid to its structure in membranes. However, recently, with the work of Ling (1965), Pauling (1961) and Miller (1961), water structure has assumed new importance in the concepts of function of cell membranes and as the site of action of certain drugs such as general anaesthetics. Pauling (1961) has adapted the theory of Frank and Wren (1957) about the structure of liquid water and applied it to the cell water. He suggests that a certain amount of cell water adjacent to cell protein forms hydrate microcrystals. These microcrystals are very unstable at body temperature and therefore are normally present in very low numbers. They are stabilized by the polar side chains of proteins or charged solutes which they entrap and by H-bonding among the water molecules which form the microcrystal. Miller (1961) advocates a similar highly ordered state of water at the surface of membranes and proteins. These ideas will be referred to subsequently in the discussion of anaesthetics.

The picture of the cell membrane presented thus far is a relatively static one. According to Kavanau (1965, 1966) this trilaminar form is actually artefact produced by the methods of preparation and fixation. In order to account for the capacity of the membrane to do work, he postulates that the lipid phase exists in the form of micelles (structured aggregates of lipid molecules) capable of reversible transformation between broad flat discs and tall, narrow pillars. Protein is present on two surfaces of the micelle; lipid-protein association is maintained by H-bonding, polar and hydrophilic attraction. Changes in the nature and concentration of cations at the polar and groups of the lipid micelle can lead to the collapse of a pillar to a discoid micelle. This collapse may be accompanied by extrusion of material through the pores which are the polar regions between triads of closely packed micelles. By means of this transformation Kavanau attempts to explain the function of the membrane such as active transport and impulse conduction. At the present time it is not possible to pass judgment on this model of the cell membrane, but undoubtedly its emphasis on the dynamic properties of the membrane should provide the stimulus for much further research.

III. FUNCTION OF CELL MEMBRANES

In nervous tissue the only membrane function which is of importance with respect to the action of drugs is the maintenance of ionic concentration gradients and electrical activity.

a) MAINTENANCE OF IONIC GRADIENTS

Na^+ is the chief extracellular cation while K^+ is more concentrated intracellularly. There are basically two schools of thought as to how these concentration gradients are maintained.

One group hypothesizes that K^+ accumulates inside cells by combining with anions in special regions of the cell while the K^+ in the rest of the cell water is in free diffusion equilibrium with the extracellular water. Ling (1965) maintains that K^+ is selectively absorbed onto the β and γ-carboxyl groups of cell proteins. The ion is then relatively fixed in the region of charged side chains of proteins and is therefore excluded from the free cell water. Membrane potentials are equilibrium phenomena determined by the density and nature of anionic sites on or near the cell surface. The concept of active transport is rejected on the grounds that the calculated energy requirement to maintain the absorbed concentration gradients far exceeds the cell's capacity for energy production.

The second group postulates that Na^+ and K^+ are free in the cell water and that membrane potentials are due to the diffusion of these ions across the membrane (Hodgkin, 1958). In the resting state the membrane is relatively permeable to K^+. The constant diffusion of K^+ across the membrane, unaccompanied by anions, creates a potential difference across the membrane, the inside being negative. The magnitude of the resting potential is approximately given by the Nernst equation $E\ (RT \div F)\ l_n\ (Ko \div Ki)$ which is approximated by 62 log extracellular $K^+ \div$ intracellular K^+. The concentration gradients are maintained by an active energy-requiring transport system.

The question of the existence of an active cation pump is of central importance to the pharmacologist, since the action of many drugs is explained on the basis of their effects on this system. Since the basis of the rejection of active transport lies in its calculated energy requirements, these calculations must be scrutinized closely before reaching a conclusion.

b) EXCITATION AND IMPULSE TRANSMISSION

The membrane may be excited either electrically or mechanically. Excitation produces a large increase in Na^+ conductance which transiently reduces the membrane potential or even reverses it, making the inside positive. A delayed increase in K^+ conductance, together with the decay of Na^+ conductance repolarizes the membrane. The shifts of Na^+ and K^+ caused by each impulse are reversed by the active transport sys-

tem. Drugs affecting this transport are found to have a greater effect on tissue during stimulation—when the transport system is most active—although the basis for this is not completely understood.

The localized change in membrane potential produced by excitation is propagated along the conducting part of the axon to the synapse or neuroeffector junction. At this point the transmission of the impulse appears to be always chemical in the human nervous system. The list of possible chemical transmitters includes acetylcholine, norepinephrine, epinephrine, dopamine, serotonin and γ-amino butyric acid. Recent electron microscopic and differential centrifugation studies have shown that acetylcholine is contained within membrane-bound vesicles which are clustered along the pre-synaptic membrane. The wave of depolarization appears to cause the synaptic vesicles to discharge their acetylcholine through the pre-synaptic membrane and the transmitter is released into the synaptic space. It diffuses across this space and attaches to the cholinergic receptors on the post-synaptic membrane. It is then hydrolyzed by cholinesterase.

The effect of the transmitter depends on the nature of the cell as well as the nature of the transmitter. Both acetylcholine and epinephrine may be either excitatory or inhibitory. The mechanism of this effect is probably a change in the chemical activity or a change in physical properties of the postsynaptic membrane leading to changes in ionic permeability which results in alteration of electrical activity. The exact mechanisms are quite unknown.

IV. PHARMACOLOGY

a) INTRODUCTION

Drugs that act specifically on nervous tissue modify either the generation, conduction or transmission of electrical impulses. The first two events involve modification of membrane permeability to Na^+ and K^+. Modification of synaptic transmission can be accomplished either by a direct effect of the drug on the pre-synaptic or post-synaptic membrane, or by altering the rate of synthesis, release, or breakdown of the transmitter substance.

A common classification of drugs according to mechanism of action is the division into non-specific and specific drugs (Ariens, 1964). *Non-specific* drugs are those which have few and usually weak reactive groups and these are capable of interacting with many constituents of the cell membrane. For their action they must accumulate in sufficient concentration and modifications of structure only affect their activity insofar as they alter this accumulation. The homologous series of aliphatic alcohols is an example of non-specific action, potency increasing with increasing length of carbon chain. A drug with *specific* action interacts specifically with a small, specialized region of the membrane which isc alled the *receptor*. The drug usually has a high capacity for ionic and H-bonding by groups with specific steric relationship as will be described below. Small changes in structure result in large changes in activity. This class of drugs may include cholinergics, anticholinergics, antihistaminics and local anaesthetics.

However, for the purposes of illustrating drug action on the cell membrane, I will classify them according to the nature of their interaction with three basic structural components of the membrane: protein, lipid and water. Undoubtedly any effect on one of the components affects the other two but most theories of mechanism of drug action implicate either protein, lipid or water as the primary site of interaction.

2. DRUG ACTION ON PROTEIN

The reaction of most drugs with membrane protein falls into the category of specific drug action and involves interaction with a receptor. The receptor theory is dealt with in detail by Ariens (1964, 1965) and the following is a brief summary of the concept.

The potency of a drug depends upon its affinity for the receptor and on its ability to produce the biological effect once it is combined with the receptor. The drug is bound to the receptor by electrostatic attraction, H-bonds, Van der Waals forces and possibly some weak covalent bonds. For sufficient interaction with its receptor a drug must have a structure complementary to that of the receptor with a significant number of H-bonding and Van der Waals atoms in such a position as to fit the corresponding atoms in the structure of the receptor (Gero, 1965). Slight modifications in the structure of the drug may result in an antagonist which still has affinity for the receptor site but no intrinsic activity (see Fig. 2). The mechanism by which interaction of drug and receptor results in biological activity is still largely

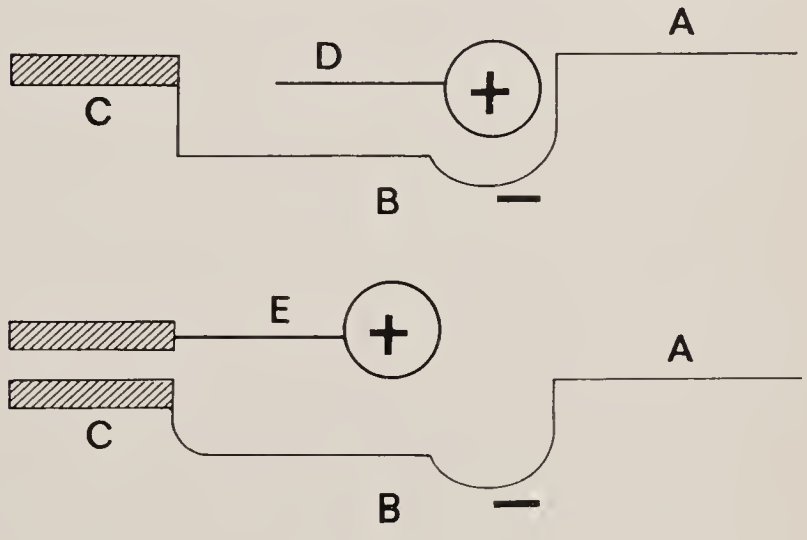

FIG. 2

A—cell surface
B—acetylcholine receptor
C—lipophilic region
D—acetylcholine molecule
E—acetylcholine antagonist containing lipophilic group
The accurate fit of the polar group of acetylcholine into the polar region of the receptor is essential for biologic activity. The lipophilic group of the antagonist allows it to bind to the receptor but prevents closed apposition of the polar regions (Burgen 1965).

a mystery. It may induce a change in the charge distribution or shape of the receptor unit which is transmitted to the surrounding molecules and results in an effect. The interaction of acetylcholine with its receptor may alter the structure of both protein and lipid phases and thus bring about an increase in Na^+ permeability by purely physical means.

Not all drug action on membrane protein need involve receptors. Some tranquilizers may act by adsorption onto the membrane and surrounding it with a monomolecular film which decreases transmembrane permeability (Seeman and Bialy, 1963). Ethanol probably affects protein in a non-specific way by virtue of its H-bonding. In this process it seems to alter the K^+ site on the Mg^{++}, Na^+, K^+-activated ATPase of brain tissue, resulting in a decreased affinity for K^+ (Israel *et al.*, 1965).

3. DRUG ACTION ON LIPID:

The importance of the lipid phase of membranes in the action of narcotics has been realized for many years. Narcotic potency was shown to correlate with solubility in olive oil (Meyer, 1899). The narcotic effect was considered to be proportional to the degree of saturation of the lipid phase of the drug. However, as Ariens (1964) points out, just because a certain physical or chemical property such as lipid solubility is found to parallel certain biological activity such as narcosis, it is not possible to conclude without further evidence that it is essentially concerned with that biological effect. Moreover, Pauling (1961) points out that any physicochemical property depending on strong intermolecular forces will be found to parallel lipid solubility and narcotic potency. For these reasons the importance of the lipid phase in drug action is not as clear-cut as it was once thought to be and much of the attention is being shifted from the lipid phase to the aqueous phase which will be discussed subsequently.

It is nevertheless possible that some classes of drugs do produce their effect by dissolving in the lipid of the membrane and altering such properties as surface tension, pore size and orientation, protection configuration and enzyme activity. Skou (1961) found that local anaesthetic potency parallels the ability of the drug to increase the pressure in a monolayer of nerve tissue lipids. He believes that the local anaesthetics act as membrane stabilizers by increasing the packing in the lipid phase, compressing pores and decreasing membrane permeability to Na^+.

4. WATER

In 1961 Pauling and Miller simultaneously but independently brought forth a theory of anaesthesia based on the occurrence of structured water in the cell. Pauling found that the potency of various non-H-bonding anaesthetics, such as the anaesthetic ethers and xenon, was proportional to the stability of their hydrate microcrystals. Furthermore gases such as xenon take part in no biologically significant reactions other than the formation of clathrate crystals. These crystals are very unstable except at very low temperatures. However, under normal conditions, they are somewhat stabilized by charged solutes. The non-H-bonding anaesthetics occupy the cavities in these crystals and add further stability to them. The effect of increasing the amount of structured water is to increase the impedance to electrical activity, presumably by impeding ionic movement. Chemical reactions may be slowed by entrapping of reactant molecules or by blocking active sites on enzymes. The main site of these actions is believed to be the synaptic region.

H-bonding anaesthetics may also ultimately function by formation of hydrate microcrystals. There is a known hydrate crystal for ethanol whose H-bonding allows it to be incorporated into the framework of the crystal.

Both Pauling and Miller believe that the anaesthesia due to cooling the body to the vicinity of 25°C is due to stabilization of these crystals. However, it is still difficult to say at present whether these crystals can be stable enough at body temperature to play a significant role in surgical anaesthesia.

V. SUMMARY

This has been a review of the structure and function of the cell membrane. The manner in which its three main components (lipid, protein and water) can be affected by drugs has been discussed in general terms with references to some of the classes of drugs that act on the nervous system. Many important problems such as the existence of pores, the mechanism of active transport and the role of Ca^{++} in membrane function have not been discussed because of limitations of time and space.

It is evident that a variety of drugs produce their biological effect by interacting with the cell membrane. These interactions range from the very specific reactions of some drugs with small specialized portions of the membrane, to the non-specific interaction of some drugs with many components of the membrane. Most of the investigations thus far have concentrated on the accumulation of the drug at its active site and the mechanism of its interaction with the membrane. Future research must be directed towards the relatively untouched question of how the drug-membrane interaction results in alteration of cellular function.

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Memory

B. Haberstroh 6T7

A simple definition of memory might be the storage of information over a period of time. However, one which is more in keeping with neurophysiological terminology, is that memory is a "set of relationships" between anatomically separated neurons that are able to reproduce a pattern of discharge after a time interval, each cell in the unit contributing some fraction to the overall expression of the memory. In this context, I wish to consider a mechanism of memory incorporating the old theories and in keeping with modern research. About 1900, Muller and Pitzecher suggested that the physiological changes leading to permanent memory became gradually consolidated as a result of the perseveration of neuronal activity during a learning process. In 1949, Hebb advocated that there were actually three phases in the formation of memory:

1. the persistence of neuronal activity after the termination of the initiating stimulus,
2. the formation of a cell-assembly unit, which presupposed that the repeated firing of a synapse led to a permanent modification in the excitability of that synapse,
3. the permanency of the growth changes which resulted from the passing of activity from one cell-assembly to another.

Then in 1958, Hydén and Pigon postulated that the true nature of memory storage was found in the structural modifications of the RNA molecules in the neurons.

From clinical experience in such conditions as Korsakoff's psychosis and from psychological experiments on memory, a dualistic theory has evolved whereby short-term and long-term memories are presumed to exist and to be governed by different set of rules.

This "modified dualistic consolidation theory" proposes that any information is initially represented by neuronal activity which in turn produces a structural modification. Evidence supports the view that short-term memory is represented predominantly by the activity of neuronal circuits and that long-term memory depends ultimately on some form of synaptic and/or neuronal changes.

Certain researchers maintain that memory involves a single mechanism with a single set of rules and particularly that no "short-term" memory per se exists. However, as we shall demonstrate the dualistic hypothesis is a more practical and acceptable theory of memory storage.

SHORT-TERM MEMORY

Short-term memory is quite labile and short in duration. The storage of this information is the pattern of reverberating neuronal impulses, called memory trace, which continue for some time after the initiating signal has stopped. Although an all-or-none impulse circulating in closed neuronal chains represents one possible mechanism for the initial short-term memory, the actual type of electrical activity which does take place remains still unknown.

(i) EXPERIMENTAL EVIDENCE

All the agents known to produce amnesia or loss of recent memory have been shown to alter the electrical activity of the brain. The administration of electroconvulsive shock (ECS.) after a learning trial markedly impairs the learning ability of rats. Similar effects have been recorded by the use of hypoxia, low temperature, and depressant drugs such as pentobarbital and ether. Approximately modified experiments on humans bear out the above results. It has been further demonstrated by ECS that the closer a seizure is to the end of a preceding learning trial, the more impaired will be the learning loss. From investigations similar to the above, the consolidation time has been recorded to vary from fifteen minutes to one hour depending on the animal species. However, in man, evidence from retrograde amnesia suggests an entirely different time scale, namely that of years or a lifetime, for the process of consolidation.

McGaugh and other co-workers have demonstrated in a series of experiments that the administration of various stimulant drugs, such as strychnine and picrotoxin, both given before and after a training trial, increases the rate at which learning proceeds. The closer the injection is made to the previous trial, the greater the improvement in performance on the succeeding trials. These same workers have enhanced the learning ability of rats by administrating a new substance—1757I.S. Because strychnine can increase the rate of firing of already active neurons, it has been postulated that the experimental results are the consequences of increased intensity of neuronal activity which in turn facilitated consolidation.

Cortical stimulation experiments have clearly illustrated the capacity of polarized cells to retain some representation of an imposed electrical pattern for a relatively long period of time. In addition, the brain has the ability to spontaneously generate temporal patterns of electrical potentials which are substantially the same as those elicited by a previous experienced stimulus. It is of interest that one can see regions relatively distant from each other with the same patterns, as if an anatomically extensive system were activated. Attempts to correlate EEG rhythm changes with short-term memory storage have been unsuccessful.

(ii) CLINICAL EVIDENCE

The consolidation of memory is inoperative in post-traumatic (retrograde) amnesia states and during the discharge of temporal lobe epilepsy. Retrograde amnesia results from the direct mechanical effects on nerve fibre tracts and the subsequent distortion of the white matter in the reticular formation and hypothalamus. In turn, focal epileptogenic lesion may impair new memory recording and yet not disturb previous learned behavior.

LONG-TERM MEMORY

The relatively permanency of memory demands a stable, long-lasting process. Accordingly, Hydén proposed four steps in the recording of permanent memory via RNA molecular coding:

1. the *specification of RNA in the nerve cell* by the first series of impulses. The modulated frequency affects the intracellular ionic equilibrium which in turn changes the stability of one or more of the four bases in the RNA molecule at a certain site. There is an exchange of bases, and when a new one occupies the space available in the molecule, the whole structure becomes stable again.

2. this new specified RNA directs the *synthesis of a specific protein molecule* which differs significantly from that previously produced by the cell.

3. the protein's response to an electrical pattern similar to that which originally specified the RNA is to rapidly dissociate and so provide a protein fragment that will react with a pre-determined complementary molecule already present in the cell. This reaction causes the *explosive release of the transmitter substance at the synapse*. At this step, two assumptions had to be made, namely, the intracellular presence of the complementary substance and the property of the protein to respond to the same electrical pattern that had previously altered the RNA.

4. the release of the transmitter *allows an information-carrying modulated frequency to bridge the synapse and so be passed along* to the next neuron and so on, according to specific anatomically patterns. The transmitter plays no part in memory storage but only facilitates the activation of appropriate neurons.

The relative immunity of the altered RNA-protein complex to further external influences is due perhaps to its binding to cell membrane phospholipids. This protects it from further electrical changes and fixes it to the cell membrane where the function of recognition of the incoming impulse is most likely to take place.

The conscious access to our permanently stored information offers many problems in explanation. How does the molecular coded pattern bring about the firing of complex and specific neuronal nets in the brain? The key to the problem arises from the hypothesis of Seclenov that the memory trace of a past sensory experience could be evoked by the recurrence of any fraction of it, even if this fraction were quite insignificant and unrelated in the desired memory. Thus the excitation of a sufficient sub-group of cells in a cell-assembly unit, would reactivate the relationship and re-entrant pathways. The discharge of the full memory group would of necessity recreate the configuration of neuronal activity which initially consolidated the system. Likewise, the cellular availability of the stored information would be the recognition by the RNA or protein molecules of the same pattern of impulses or synaptic activation which established the original pattern. Random excitation of cells in a memory unit would not necessarily disrupt the stored memory if these impulses were not sustained for the minimum period postulated as necessary to effect the macromolecular alteration.

The reactive protein molecules are manufactured for life according to RNA specifications. Thus each neuron perpetuates within itself a sufficient number of unique models of RNA and proteins. By virtue of the modulated frequency, the same permutation of RNA molecules must be present in all the nerve cells that had cooperated in storing a specific single memory. Such a versatile foundation for multiple storage does not require strict localization within the CNS but can be quite diffuse.

Alternatively to the above, it has been proposed that all possible RNA nucleotide sequences and their correspondingly coded proteins are already available within the cell. An incoming pattern of electrical impulses would select or re-orient some of these limited and preselected molecules at the expense of others. A third view put forth is that as the intracellular electrolyte concentration is altered by sustained reverberating activity, a change would occur in the carbon-to-carbon bond angle of RNA. Such changes in spacing on the RNA template would alter the amino acid species that would fit into that place. The rate of protein synthesis is entirely dependent on the achievement on the appropriate concentration of amino acids on the template.

With the above presentation of the modified, dualistic consolidation theory, I should now like to set forth certain experimental works which seem to uphold the molecular specificity of memory and also which attempt at anatomical localization of memory storage.

(i) BIOCHEMICAL EVIDENCE

It has been suggested that if memory patterns are the structural changes related to RNA, depolymerization by ribonucleases should destroy these memory patterns as well as the learned behaviour which depends on them. Some evidence for such an effect has been found.

Experimental studies have shown that increased functional demands are followed by increased RNA produc-

tion. Mild physiological stimulation, such as rotation of the head, has resulted in quantitative changes. RNA and protein concentration increased in the neurons as did also the respiratory enzymatic activity. Similar kinetic studies revealed that the neuron reacted by highly increasing the capacity of the electron-transporting system, thereby reflecting an increased energy consumption as a function of the stimulus. RNA synthesis and changes in base ratios were also induced by chemical substances. The use of the MAO inhibitor Tranylcypromine (Parnate) and also the anti-depressant Imipramine (Tofranil) gave the same results as above. Whether these two drugs affect memory has as yet not been established.

In these experiments, the exact reverse in base ratios and cellular activity was noted in the glial cells. The complex interrelationship between neurons and glial cells and their biochemical interdependence has raised the possibility that the glial cells might act as a regulatory feed-back system. They would provide the energy needed by neurons to regulate the frequencies due to neuronal stimulation as well as control the flow of substrate from the glia to the neurons.

(ii) EPILEPTIC MIRROR FOCUS

The whole concept of the consolidation of neuronal activity into permanent storage is seen in the experiment of the epileptic mirror focus. In it, normal neurons in the opposite hemisphere are exposed to the bombardment from the primary epileptic lesion, the secondary site corresponding to the termination of callosal fibres from the primary focus. Initially the secondary site will discharge only when the original focus discharges. However, after a variable period of time, depending on the species, the secondary focus develops a permanent alteration of excitability such that it is capable of self-sustained, paroxysmal epileptiform discharge. This is true even when the primary focus is not discharging for some time and/or after months of inactivity as a result of cortical isolation. Changes indicative of abnormally high concentration of RNA occurs in the cells at the site of the secondary abnormally discharging focus. Thus the mirror focus can not only learn to behave in terms of paroxysmal discharge, but also to remember this behavior after months of inactivity.

(iii) STRUCTURAL LOCALIZATION

The structure of the CNS as a whole and with respect to individual cells must also be taken into consideration with this problem of memory storage. This is most evident in experiments conducted by Penfield whereby electric stimulation of subcortical regions in the temporal lobe of patients elicited whole complicated memories.

Because states of extreme arousal seem to preclude storage of any but immediately associated stimuli, the reticular formation in its most general sense has been suggested by many workers to serve as a selective filter or sorting system. By this, stimuli are looked after and perhaps put into a labile short-term memory for ultimate disposition to the cerebral cortex for analysis and discrimination.

With its free connections with all parts of the cortex and corpora mamillaria, the hippocampus might represent a boosting, feed-back, or replaying mechanism. It could contribute to the essential stimulus with associated ideas and feelings which are so important in consolidating memories. Cortical operation requires a strong play-back action from the hippocampal system before the cortical memory patterns can be consolidated sufficiently for future recall.

Much work has been done to try to localize the site of memory pattern formation and the interhemispheric transfer of such within the cerebral cortex. This latter problem was studied by the use of splitbrain preparations. By this, sensory information, e.g. visual, is channeled to one cerebral hemisphere by cutting the optic chiasm antero-posteriorly in the midline, and also other midline fibre tracts, particularly the corpus callosum. By severing fibres in appropriate places, it has been shown that visual discrimination acquired on the one side could be transmitted and stored by the other side via the posterior half of the corpus callosum. In monkeys, it can be shown that transfer of information from one hemisphere to the other occurs only with simple discrimination and that the transference is not spontaneous. There is no conflict in learning two opposing types of trained responses presented to each half of a split-brain preparation. The memory pattern of one side gains ascendancy and the activity of the animal is controlled by it, while the other side is suppressed.

In monkeys, visual discrimination, learning, and response performance has been selectively and transiently impaired by stimulation of the infero-lateral temporal lobe. Similar results were also obtained with stimulation of the caudate nucleus and/or the sulcus principalis region in the frontal lobe.

(iv) CLINICAL AND PATHOLOGICAL CORRELATION

There are many clinical syndromes with pathological correlations that implicate certain anatomical structures in permanent memory storage. When defects occur, careful analysis of performance often suggests an impairment that is not a loss of the memory pattern per se, but rather a failure in the organization of material so that initial perception, registration, and recall are almost equally affected.

It has been demonstrated that men with parietal lobe lesions show an abnormal interaction between two successive pressure sensations, so that the second of the two tactile stimuli is markedly overestimated. A corresponding abnormal interaction was observed for visual

stimuli with occipital lobe lesions. The implication is that the brain was not able to compare the two stimuli because of failure to store the initial stimulus. [In patients with pure and subcortical visual agnosia, the lesion is located in the medial occipito-temporal (lingual) gyrus in the dominant hemisphere.]

Patients with bilateral destruction of the hippocampal complex manifest interesting findings. These patients develop an isolated memory defect with the preservation of other cognitive functions. They have great difficulty in establishing lasting new memories, despite well-preserved immediate memory span. The explanation for the findings is that storage merely fails to take place because an important locus or connection for this process has been damaged. The occurrence of retrograde amnesia with hippocampal lesions indicates that the latter structure is essential not only for forming new memories but also for the temporary storage of memories before permanent storage takes place elsewhere.

Korsakoff's psychosis is characterized by a variable inability to learn and remember new events with or without associated confabulation. The memory is disproportionately disturbed, for with stress the person may perform adequately on a standard intelligence test yet in a few minutes forget the whole incident. Although recent memory suffers the most, even remote memory is defective in all but the mildest cases. This well-known disease appears to be related neurophysiologically with that associated with hippocampal lesions. The lesions in Korsakoff's psychosis are symmetrically located in the medial nuclei of the thalamus, the paraventricular region in the hypothalamus, the mammillary bodies, the terminal parts of the fornices, and the region around the aqueduct of Sylvius. The abnormalities involve the destruction of both nerve cells and myelinated fibres, with hemorrhage usually being found in the affected areas.

Similar syndromes can be produced by vascular, neoplastic, infective or pathological processes in the above mentioned parts of the brain or in the rhinencephalon. According to the consolidation theory, this loss to form long-term memories can be explained by supposing that neuronal activity fails to produce a synaptic change either because of a loss of the ability to make neuronal associations in the neurons or by their destruction. In fact any of the diseases which are localized to the hippocampal convolutions, the fornices and the medial aspects of the diencephalon share the property of reducing in a general way the capacity of man to learn newly presented material and of abolishing memories established long before the onset of the disease.

In general, memory function depends on a mechanism which integrates the activity of neuronal assemblies of the diencephalon, the hippocampus, and the cerebral cortex. At the neocortical level, impairment of general memory function appears to be more or less in proportion to the extent of the lesion. From clinical studies, it is evident that there are also special memory functions which involve cortical mechanisms lying in close proximity to the tactile, visual, and auditory centers in the brain. The relation of the general memory mechanism to the production and retention of specific memories is at present unknown, but it appears likely to depend more on cellular interrelations than on molecular changes within the nerve cells.

CONCLUSION

At present, no one can state with certainty whether or not the specific alterations produced by a learned experience is to be found in single nerve cells, in the structure of the cells, i.e. in synapses, in patterns of terminal buttons, or in carrier ribonucleoproteins, or in terms of the interrelationship between groups of cells in the cerebral cortex and diencephalon. However, the combination of Hebb's and Hydén's proposals to establish two types of memory storage offers the best answer. Thus information storage is a function of neuronal electrical reverberation and of specifically structured macromolecules which are altered by the resultant intracellular ionic changes.

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Recent Advances

The Synapse As A Model For Information Processing And The Learning Process

The tools have not yet been created that will enable man to gain a fundamental understanding of the workings of the human brain. The EEG, at best, is but a witness to a massive information processing system and so far has proven totally inadequate in trying to separate even one mechanism from the rest. Three branches of science have established certain facts regarding brain mechanisms and any theory must satisfy these facts. Psychology is concerned with the overall behaviour of the system; mathematics helps define whether proposed laws of synaptic variability will lead to the aforementioned behaviour; neurophysiology describes the actual biological events which must occur in order to effect behaviour.

In a recent paper attention has focused on the synapse as the functional unit in information processing and the learning process (1). Consider a person in a particular environment. He becomes aware of his surroundings via sensory nerve endings. These endings are, in effect, transducers for as they become aware of heat, pain, pressure, etc., they are stimulated in some way to generate a potential difference or electrical signal which ultimately enables the person to respond to the stimulus and thus cope with his environment. The fact that a certain stimulus generates a potential difference is in effect an item of data or piece of information. The fact that it is transmitted as an electrical signal, even though qualitatively there is no difference in electrical signals, is of little consequence, for when the signal reaches its ultimate destination, it is somehow interpreted to mean heat, pain, pressure, etc. If the human body were to react to every single stimulus it received there probably would not be any time left for purposeful function. Rather than deny the existence of stimuli it is more correct to assume that there are extremely complex relationships among stimuli wherein they can modify each other, prevent transmission of a given stimulus, or alter the final response. In other words the information received from a transducer must be compared to information received from other sources and the final product, either changed or unchanged from the original, continues along the information transmission pathway. This is information processing. Transmission along the "cable" (axon or dendrite) is virtually an automatic process once the necessary stimulus has been achieved, however there is not a continuous path from the beginning to the endpoint and the original signal must in some way pass across a space from one cable to the next. This space is the synapse and represents the junction between axon and axon, axon and dendrite, or axon and muscle fibre. The electrical signal is converted to a chemical form in order to pass this space. Because a change is taking place many factors can influence the final result and so it is that signals received from other sources can modify the final chemical form of the original piece of data either qualitatively, quantitatively, or both. The piece of data after final modification represents a particular "pattern" and perhaps as receptors farther along come to recognize this pattern and react in a predictable way, the process of learning is being carried on. Thus it is reasonable to think of the synapse as the functional unit in information processing and learning.

BASIC MECHANISM OF THE SYNAPSE

For the purposes of description consider the end of the neuron from which the original signal enters the synapse as the presynaptic site and the area of the membrane which receives the signal after the space as the postsynaptic site. When the wave of depolarization reaches the presynaptic site it causes a release of excitatory transmitter substance (E.T.) into the synaptic space. The E.T. transverses the space and impinges upon the postsynaptic site. When the permeability of the membrane is changed so that depolarization occurs transmission of the signal continues. If the E.T. acts in some way to prevent depolarization from other sources then it is said to act in an inhibitory capacity. It is thought that excitation as depolarization occurs at all three possible sites, axo-axonic, axo-somatic, and axo-dendritic, whereas the inhibitory influence is effected chiefly at the first two (2). In addition to the inhibitory effects produced by other sources, there must be some mechanism which eventually prevents the presynaptic site from emitting further E.T. for not every presynaptic site has axons ending on it expressly for the purpose of inhibition. Once the postsynaptic site has discharged, the chain of transmission has been continued and it is no longer necessary to keep putting out E.T. Thus, if there were a substance which prevents the presynaptic site from emitting E.T. after the postsynaptic site has fired then it would be possible to control the functioning of the synapse. This expedient of regulating the E.T. according to what is happening at the postsynaptic site is called feedback. There is evidence that the postsynaptic sites release an inhibitor transmitter substance (I.T.) immediately following depolarization (3). This substance produce an increase in the K^+ and/or Cl^- ion conductances of the membrane on which it impinges and thus accelerates the rate of return to the resting potential. The concentrations of free I.T. and E.T. would decrease as a result of rapid removal and degradation. According to present knowledge acetylcholine and glutamic acid are known to act as E.T.'s and γ-aminobutyric acid as an I.T. (4). The biogenic amines, serotonin, dopamine and noradrenaline also probably act as transmitters in the central nervous system. However, in no instance have these substances been shown operative at a particular synapse let alone all synapses.

FACTORS AFFECTING E.T.

E.T. is manufactured in the axon by enzymatic action on certain precursor substances. Some of these precursors must come from the extracellular environment.

E.T. exists in two forms, bound and free, and undoubtedly an equilibrium exists between the two. As E.T. is manufactured at the nerve ending it must in some way be transported to the membrane from which it will eventually be released, and so it is reasonable to assume a gradient within the volume of the nerve endings. In reality several gradients could occur, one for the free form of E.T., one for the bound form, and one for the precursors. At a maximal level for this gradient the already formed E.T. may inhibit further E.T. formation. When this stops the flow of extracellular precursors coming into the cell would probably also stop. When the stimulus representing an item of data reaches the membrane it affects the permeability thus enabling some E.T. to be released, the free form first. There is always some E.T. in the synaptic cleft without causing depolarization of the postsynaptic site and so it is reasonable to assume that the quantity of E.T. is important. The amount of E.T. required to cause depolarization can be thought of as a functional unit or quanta and designated as the end plate potential (EPP). The greater the stimulus the more EPP will be released. By the same token, if the stimulus is continuous or powerful enough, all of the formed E.T. (free and bound) may be released. As time is required to synthesize more E.T., less and less E.T. will be emitted per stimulus so that ultimately the presynaptic site becomes exhausted and non-functioning.

THE LEARNING PROBLEM

Learning in its most general terms can be thought of as *connectivity* or direct relationship between pre- and postsynaptic elements. In other words, "how can the use of a particular synaptic connection between particular neurons produce an enhancing effect so that successive excitory afferent signals arriving at the same ending become quantitatively more important relative to those from synaptic connections in the same microanatomical field which have received less use?" (1). Theories explaining the establishment of connectivity must also account for a progressive increase in relative importance of a particular item of data and for regressive loss of dominance with disuse. Thus there are two types of connectivity between neural elements — temporary and permanent. Perhaps permanent connectivity may imply memory. Three factors are important in the establishment of connectivity:

(1) transmitter action and ion movement (physiological)
(2) total amount of surface apposition and transduction at a synapse (growth)
(3) the genetic expressivity which determines the degrees of similarities of surface properties of cellular elements at the synapse and their affinities for each other (genetic)

PHYSIOLOGICAL FACTORS

The description of transmitter movements and the basic mechanism of information transmission across the synapse have been discussed previously. It remains to establish further ramifications of this scheme. The postsynaptic site releases I.T. which is responsible for the feedback element. I.T. can affect both the pre- and postsynaptic sites and thus plays a role in limiting presynaptic excitation as well as allowing the membranes to become repolarized more quickly. This means that more items of data can be transmitted in a given unit of time and because the postsynaptic membrane can respond more quickly there develops a potential discriminatory capacity.

Further research will be required to determine if, when I.T. is deposited on the presynaptic membrane, it is deposited only on the site which has become depolarized or on all presynaptic components which end on the particular postsynaptic site. If the latter is indeed the case then it follows that in the immediate future a greater stimulus than normal would be required to discharge those membranes in the resting state which would now be covered with I.T. Because this membrane is not depolarized the processes which normally come into play in removing I.T. may be arrested or slowed down and this will potentiate the I.T. effect. This all implies that there is a decreased probability of receiving information from one of these sites with a loss in connectivity. By the same token the particular presynaptic site which had become depolarized assumes a relative increase in importance as a source of information at that synapse. All of these changes are only temporary and by their very nature are subject to change, however in the total picture they play a role in establishing the synapse as a learning site.

GROWTH FACTORS

The larger the area of contact between pre- and postsynaptic sites the more likely a piece of information will be transmitted across the synapse. The rate of growth, if such actually occurs, would vary in some manner with the number of impulses transmitted. It is necessary to inquire how impulse transmission might affect rate of growth. The growth materials are most likely supplied by the glial cells (5). In addition to the actions already ascribed to I.T. it may act in some way to facilitate the availability of materials for growth. In the absence of I.T. this facility would be lost. Also a control mechanism may be operating whereby there is a free flow of materials between neuronal, extracellular, and glial compartments only when both the pre- and postsynaptic sites are depolarized. With the aforementioned mechanisms operating the quantity of material available for growth is a balance between synthetic and degradative reactions In the absence of pre- and postsynaptic depolarization atrophy would occur and similarly if the two sites were used often growth would occur. Increased growth and surface area of contact leads to increased connectivity for a given impulse arriving at the larger presynaptic site would cause more E.T. to be released.

GENETIC FACTORS

Thus far the membranes at the pre- and postsynaptic sites have been relegated a rather passive role. Undoubtedly they play an important part in the information processing network. Surfaces can either attract, repel, or have no effect on each other. E/M studies have shown the membrane to be a phospholipid layer sandwiched between two protein layers. The ability to manufacture proteins and lipids is under genetic control as are the "instructions" for putting them together to form a membrane. A particular combination of proteins, especially in the surface layer, will exhibit a unique set of properties which in part could account for the attraction or repulsion mentioned above. It may be best to think of a particular protein configuration as a mosaic of different structures which in some way represents specializations of surface areas. Such differences in cell surface configurations have been noted in light and electron microscopic studies(6). To develop the synaptic model further it is necessary to postulate a flexibility in the mosaic of surface proteins, i.e. the ability to change in different environmental conditions. In this way if certain changes remain permanent it is possible to conclude that local environmental conditions will affect genetic control of surface properties.

It is necessary to examine how, when cells process information, the surface properties become very specific. In the embryonic development information is transferred when one cell comes into contact with another. It is postulated that more complex interchanges can occur, i.e. RNA, DNA, proteins, and thus both contacting walls could synthesize constituents which were originally characteristic of only one of them. This response to the environment could then lead to selective activation (by repression, derepression, or a combination of both) of particular genes specifying the structures of variant classes of substances which might be important in determining cell surface properties which are relevant to the adhesiveness of cells. Messenger RNA is thought to play an important role as the transfer material causing the recipient environment to promote its own production while directing the synthesis of a substance which itself becomes part of the mosaic or is an enzyme in the production of such a substance. As the surface properties become more specific there develops a connectivity between membranes and the two are drawn together increasing the contact area. This increase in likeness between two surfaces is proportional to the amount of material exchanged, which is proportional to the strength and frequency of stimulation.

LEARNING AND MEMORY

When a particular synapse is fired, changes take place for some time after the initial event and in this respect the synapse is said to exhibit a memory. The physiological factors are completed in a matter of milliseconds, the growth factors in minutes, and the genetic factors in hours to years. The act of remembering is thought to be due to the activation of a closed circuit of neurons causing repetitive firing of the synapses between members of the chain. The greater the number of closed circuits responding to a given stimulus the greater will be the probability of rapid and efficient information processing and hence the more effective would be a subsequent response to a particular pattern. Many factors act to interrupt this closed loop from continuing to function. One synapse in the loop will have a greater threshold than the others and until this synapse is fired the loop will not operate. The parameters describing the synapse must be such that the synapse will have to be fully repolarized before firing again. If this is not the case the synapse will not be able to fire and the closed loop will not continue to function. Finally there are a host of complex relationships between the synapse and its environment and some of these most likely act to cause incoordination and discontinuation of the loop.

When a synapse "learns" there are two modes which it can follow, one inhibitory and facilitatory, the other pathological. In the former the learning process would result in more or less stimulation, respectively, being required to fire the synapse with the highest threshold. Pathological learning is essentially destructive in nature. The result would be sufficient disorganization in synaptic function so as to cause the circuits which depended on these synapses to cease functioning.

CONCLUSION

This article has attempted to present a model of the synapse which may explain some of the mechanisms involved in information processing and learning in the nervous system. In model building it is necessary to begin with gross assumptions in an effort to explain one or two observable facts. As information is learned from the model it soon outdates itself but leads the investigator to a new model and a higher level of sophistication. Thus there are many shortcomings to the model presented in this article but if it stimulates one new thought or one new insight it will have fulfilled its purpose.

W. Cass 6T8

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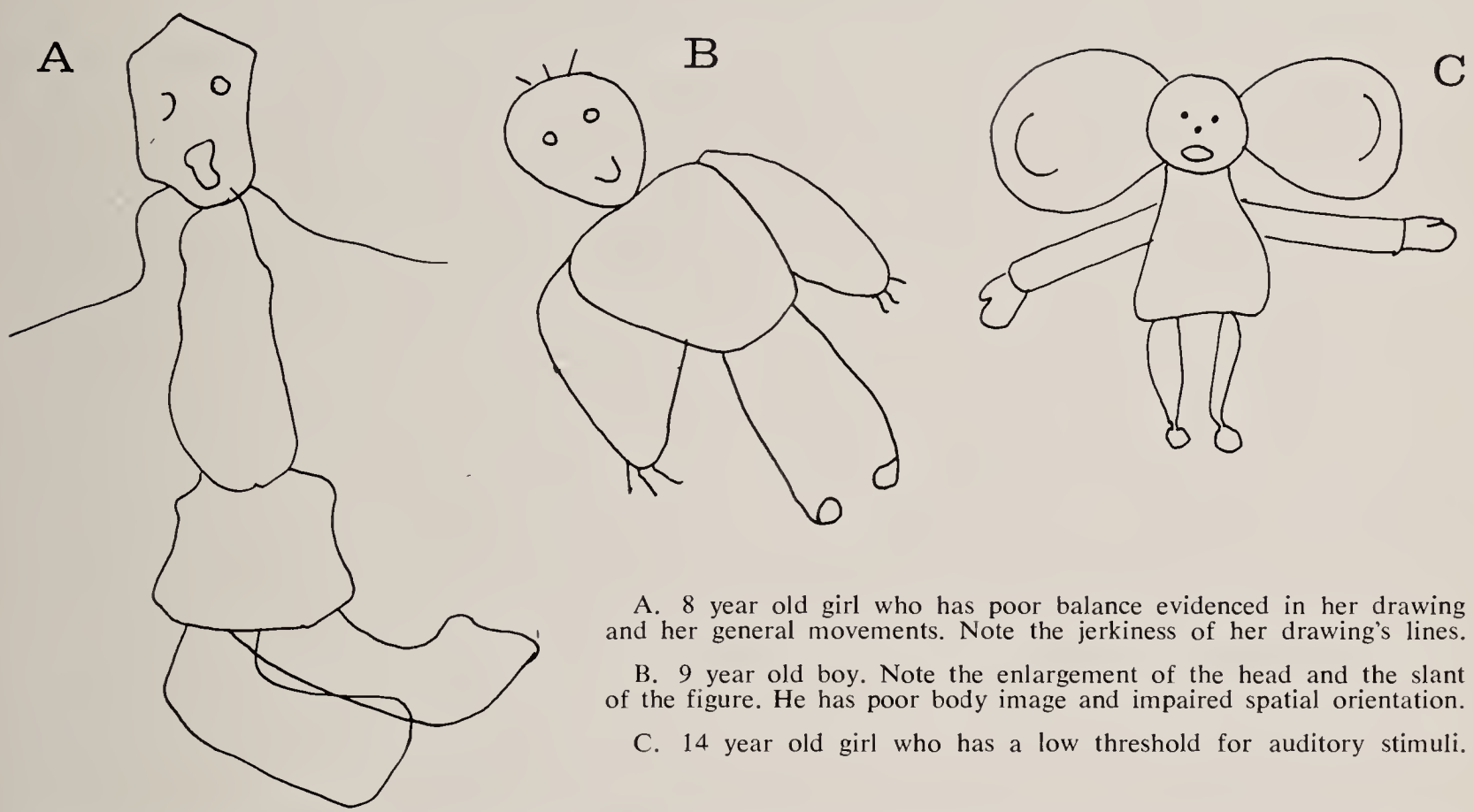
Minimal Brain Dysfunction And Learning Disabilities In Children

P. Carlen 6T7



A. 8 year old girl who has poor balance evidenced in her drawing and her general movements. Note the jerkiness of her drawing's lines.

B. 9 year old boy. Note the enlargement of the head and the slant of the figure. He has poor body image and impaired spatial orientation.

C. 14 year old girl who has a low threshold for auditory stimuli.

These drawings are examples of the 'Draw-A-Person-Test', used for estimating the degree of distortion in the body image. The perceptually impaired child has difficulty in accurately relating elements of the physical world to his self. He has trouble in size discrimination, spatial, and time orientation. Of course, some have impaired fine motor coordination preventing them also from drawing at their expected level.

CASE HISTORY

Johnny S. seemed to be a normal child, although he was a bit clumsier than his playmates. The trouble became most evident when he entered kindergarten. His teacher said that he was the sloppiest dressed child in the class. He was very restless and easily distractable. In winter time he could never put on his galoshes or mittens correctly. He talked quite loudly and got on poorly with his classmates. Grade I was even worse. Although seemingly bright, rarely did he follow directions well. His printing and drawing were atrocious. He was inattentive, hyperactive, and talkative. In desperation, the teacher contacted his parents to determine what type of home situation existed that might produce such an emotionally disturbed child. To her surprise she found two concerned, reasonable, and intelligent parents. The child was referred to a child psychiatrist, who referred the child to a paediatric neurologist. Their unanimous diagnosis was minimal brain dysfunction with a learning disability. Instead of failing grade I, or being put in a class for emotionally disturbed or retarded children, Johnny S. was given special remedial training for his handicaps by qualified teachers and psychologists. He was eventually able to succeed in school and to have normal relationships with his classmates.

DEFINITION

"Under the term minimal brain dysfunction and learning disabilities shall be those children within the normal intelligence range who display learning and/or behavior difficulties ranging from mild to most severe. These may be due to subtle deviations arising from genetic variations, biochemical abnormalities, perinatal brain insults, and/or illnesses and injuries sustained during the years critical for the maturation of those parts of the central nervous system having to do with perception, language, inhibition of impulses, and motor control."[1]

PATHOGENESIS

It has been estimated that anywhere from 5-20% of younger school-age children have this disorder. With early diagnosis and treatment, most of these children who might otherwise be lost to classes for the mentally retarded or the emotionally disturbed, or become early school dropouts, can have the opportunity to fulfil their

intellectual potential. Previously, the majority were classified and treated as emotionally disturbed or mentally retarded.

Rarely do these children demonstrate obvious neurological disease. They have behavioral, perceptual, and learning problems which may secondarily provoke emotional disturbances. In about 50% a history of possible brain damage can be elicited. These include:

temporary anoxia at birth
traumatic delivery
prenatal intra-uterine haemorrhage
arrested hydrocephalus
dehydration of the infant
subdural haematoma
accidental head trauma
meningitis
encephalitis
lead intoxiation

Sometimes there is a positive family history implicating a genetic irregularity. Additionally, children with definite cerebral problems such as epilepsy, and spastic paraplegia, often have learning and perceptual disorders. A similarity has been noted between children with known brain damage and those without known damage who have perceptual disabilities. Investigators have found a positive correlation between pregnancy complications and viral diseases in children under three, and the later manifestations of this syndrome.

CLINICAL FINDINGS

Minimal brain dysfunction in children has a varied spectrum of manifestations, each child exhibiting his own unique signs. If severe, this syndrome becomes apparent in the first few years of life, and if mild, in the early grade school days. The following are the symptoms and signs usually sought:

1) specific learning deficits—e.g. reading impairment, poor spelling, difficulty with abstraction in whole-part relationships;
2) perceptual-motor deficits—i.e. limited visual-motor coordination, difficulty with printing and drawing (see figure), poor physical coordination;
3) hyperactivity—a classical finding;
4) emotional lability, impulsiveness or lack of control;
6) often equivocal or "soft" neurological signs; i.e. transient strabismus, nystagmus, dysdiadochokinesis, mixed and confused laterality, general awkwardness;
7) history or presence of a speech defect;
8) borderline normal or abnormal EEG patterns.

To finalize the diagnosis, a measure of the child's higher nervous function is necessary. Of most value is the Wechsler Intelligence Scale for Children (WISC). In this test children may demonstrate one of the following:

i) scattered low scores in the verbal and/or performance scales;
ii) verbal I.Q. 15 to 40 points greater than performance I.Q.;
iii) performance I.Q. 10 to 30 points greater than verbal I.Q.

Low scores are also found in digit span and block design tests. Auditory memory, picture recognition tests, and specially graded oral reading exercises are also used for diagnosis.

THEORETICAL CONSIDERATIONS

Clements and Peters state, "When the fantastic complexity of the brain is considered, with its myriad of interlocking circuits and groupings of circuits, it is not surprising that in the presence of any disorder of stimuli-monitoring, that each child should manifest a unique cluster of symptoms and that he should be handicapped in learning and adaptive behavior, if the environment is sufficiently trying relative to the magnitude of his defect." They feel that perceptual defects are probably due to a decreased capacity to receive, hold, scan, and selectively screen out stimuli in a sequential order. Clements says that the behavioral irregularities, learning disabilities, and visual-motor-perceptual problems should be accepted as valid, meaningful neurological signs which represent disorganized brain functioning at the highest level. For most of these cases no specific pathological or biochemical abnormalities have been found. Glaser and Pincus point out that this syndrome is evident in children with psychomotor epilepsy. They ascribe their abnormal nonconclusive behavior to a possible subictal (subconclusive) excitation of the deep temporal, pararhinal, and diencephalic portions of the limbic system. Penfield says that the temporal is concerned among its other functions, with the comparative interpretation of perceptions and the conscious analysis of their significance. Presently there is a great tendency to accept the minimal brain dysfunction disorder as an organic entity.

TREATMENT

Without proper treatment the perceptual and learning defects will merely compound themselves; however the hyperactivity spontaneously recedes by the age of fifteen. Instead of repeated failures in school, or institutionalization with the mentally retarded or the emotionally disturbed, these children, if diagnosed and treated early, are allowed to progress almost as fast as their peers. Thus severe emotional disturbances secondary to their frustrations in school and with their playmates are bypassed. These children are taught in a low-stimulus environment by specially trained teachers using as many sensory approaches to the brain as possible. For example, a young child learning the meaning of "apple" would touch it, draw it, see it, relate it to other concepts such as "tree", and hear the word spoken. They play sound,

word, and matching games. They work with blocks and puzzles. Those with motor apraxias do balance, co-ordination, eye-hand, body-concept, and maze exercises. In these special schools each child is taught at his own level. If his attention span is 5 minutes, then every 5 minutes a new form of lesson is introduced. After 1 to 5 years they can return to a regular public school and function adequately. Family counselling is also used to enable the parents to give their child a more suitable environment in which to develop. Certain drugs such as thioridazine (Mellaril), amphetamines, and chlorothiazide (the mechanisms of the last two are mysteries) are often helpful in decreasing hyperactivity, irritability, and in increasing span. If a specific organic entity is found such as an irritative focus producing psychomotor epilepsy, specific treatment (i.e. surgery) is applied.

SUMMARY

Diffuse as the manifestations of minimal brain dysfunction are, it has been shown in the past 10 years to be a definite, treatable, clinical entity, with most probably an organic basis. Since it affects approximately 10% of the younger school-age population, it is essential that the profession be aware of its existence. This syndrome is an example of poor coordination and integration of higher nervous activity. However the underlying mechanisms of minimal brain dysfunction will remain a mystery until neurophysiologists are able to gain a much deeper understanding of the actual nature of thought processes.

ACKNOWLEDGEMENT

Special thanks to Mrs. Doreen Kronick, President of the Canadian Association for Children with Learning Disabilities.

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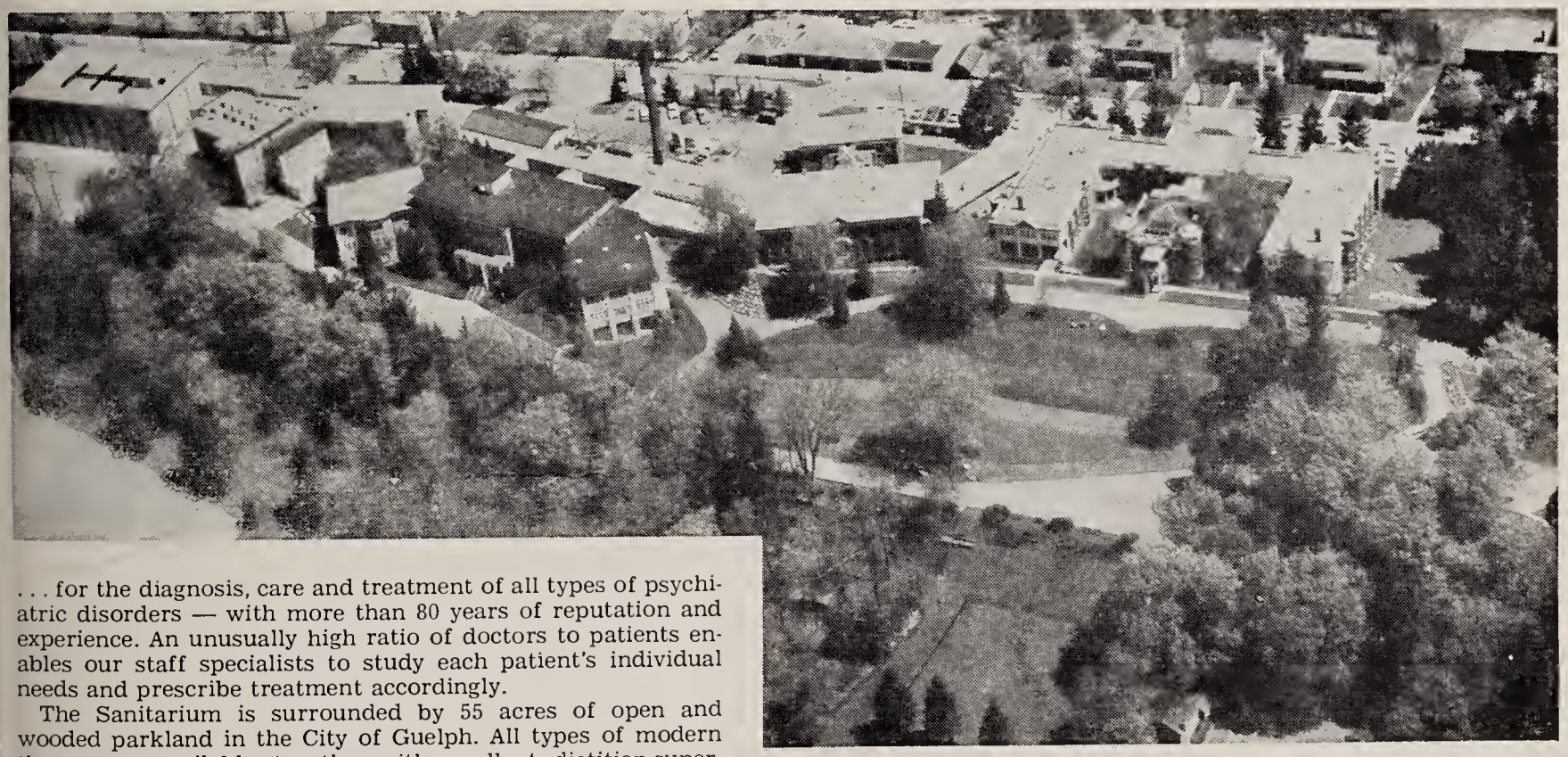

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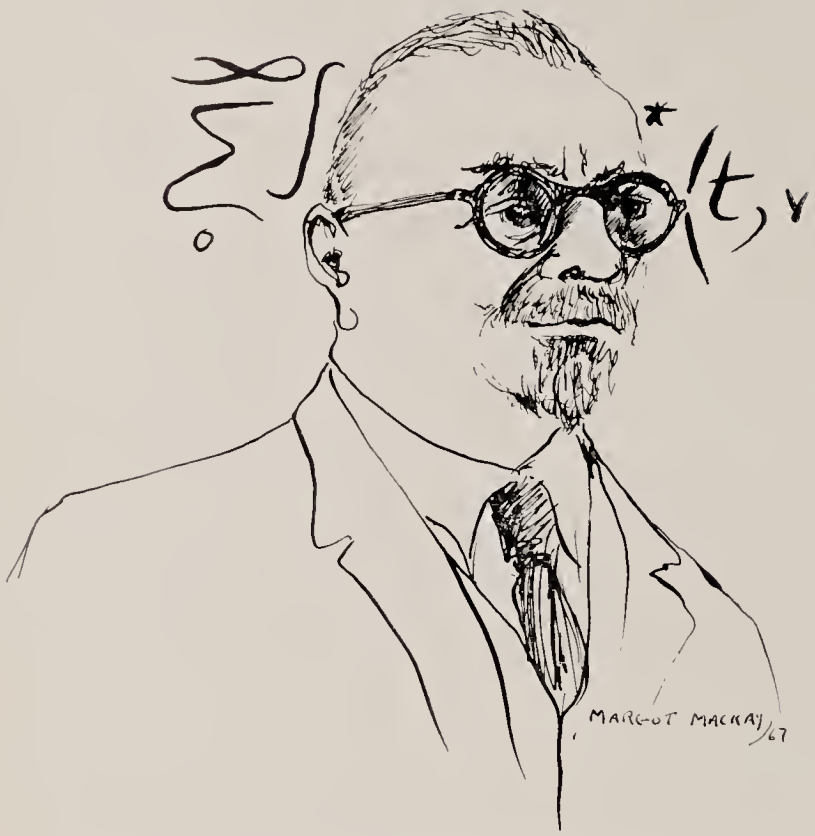
Norbert Wiener (1894-1964)
The Father Of Cybernetics



> I read one scientific article that has had a direct influence on my present work. . . . It contained a very sound account of the progress of a nerve impulse along a nerve fiber, as a consecutive process of breakdown, analogous to the consecutive fall of a train of blocks rather than to a continuous electrical phenomenon. I remember that the article excited in me the desire to devise quasi-living automata, and that the notions I acquired from it survived in my mind for many years until they were supplemented in my adult life by a more formal study of modern neurophysiology.[1]

The interval between reading the article at the age of seven and beginning a study of neurophysiology was filled with numerous interests and accomplishments sufficient to occupy two lives. No one would dispute the fact that Norbert Wiener was unique in every way from the time of his birth in Missouri in 1894 until his death in 1964. His father, a Russian Jewish immigrant, educated him at home until he was nine years of age. At eleven he entered Tufts College and graduated at fourteen with a degree in mathematics and an intense interest in zoology. Wiener was deterred from entering medical school because of his youth and took an almost antithetical pathway into the study of the philosophy of mathematics and mathematical logic. At eighteen years of age he obtained a Ph.D. from Harvard, studying under Santayana, and then did post-doctoral work with Bertrand Russell, then one of the world's foremost mathematicians, at Cambridge. It is a curious fact that it was Russell, the mathematician turned philosopher, who directed Wiener from philosophy back to pure mathematics.

Wiener's life work can be divided roughly into three phases of which pure mathematics was the first. He believed that mathematics was an advantageous study in that it

> . . . is a field in which one's blunders tend to show very clearly and can be corrected or erased with a stroke of the pencil. It is a field which has often been compared with chess, but differs from the latter in that it is only one's best moments that count and not one's worst. A single inattention may lose a chess game, whereas a single successful approach to a problem, among many which have been relegated to the wastebasket, will make a mathematician's reputation.[1]

During his early career Wiener found the life of a mathematician rather arduous; however, the period while he was an Encyclopedia Americana staff writer, in 1918, and a Boston Herald reporter, in 1919, emphasized to him that his field was definitely mathematics.

In 1923 Wiener found a position at the Massachusetts Institute of Technology where he remained for the duration of his career. Until 1933, when his major work on Fourier analysis was published, Wiener was the young enthusiast wound up in many of the mathematical and physical problems of the day. It was in 1933 that Wiener met a Mexican physiologist named Arturo Rosenblueth. Their friendship was immediate and evolved about the conviction that science should be a collaborative effort. This alliance reawakened Wiener's interest in neurophysiology, and

> Ultimately the theme of the many discussions which Rosenblueth and I had privately and in our seminar came to be the application of mathematics, and in particular of communication theory, to physiological method. We laid out a policy of joint effort in these fields for a future when we might work closer together.[2]

Wiener rose above the barriers between the sciences because he realized that

> If the difficulty of a physiological problem is mathematical in essence, ten physiologists ignorant of mathematics will get precisely as far as one physiologist ignorant of mathematics, and no further. If a physiologist, who knows no mathematics, works together with a mathematician who knows no phy-

> siology, the one will be unable to state his problem in terms that the other can manipulate, and the second will be unable to put the answers in any form that the first can understand. . . . The mathematician need not have the skill to conduct a physiological experiment, but he must have the skill to understand one, to criticize one, and to suggest one. The physiologist need not be able to prove a certain mathematical theorem, but he must be able to grasp its physiological significance and to tell the mathematician for what he should look.[3]

Previous research and lecture commitments prevented Wiener and Rosenblueth from working together for ten years. This period saw the second phase of Wiener's career and was one of expansion of theory to practise. His work consisted of developing mathematics on the principle of feedback for the building of computer systems. This work led into the final decisive phase of Wiener's career in 1943 when it excited the observation that

> . . . the apparent equilibrium of life is an active equilibrium, in which each deviation from the norm brings on a reaction in the opposite direction, which is of the nature of what we call negative feedback.[2]

Wiener came

> . . . to regard the nervous system in much the same light as a computing machine . . . I managed to get a group of neurophysiologists, communication engineers, and computing-machine men together at Princeton for an informal session, and I found on the part of each group a great willingness to learn what the other groups were doing and to make use of their terminology . . . All of them found that the term 'feedback', which had come from the electronics engineer and which was extending itself to the servomechanism man, was an appropriate way of describing phenomena in the living organism as well as in the machine . . . This meeting I may consider the birthplace of the new science of cybernetics or the theory of communication and control in the machine and in the living organism.[2]

Wiener derived the term "cybernetics" from the Greek word "kubernētēs" meaning steersman.

In 1944 Wiener joined Rosenblueth in Mexico to begin their investigations. They studied clonus, "the tonic, clonic, and phasic contraction in epilepsy, and . . . the tonic spasm, beat, and fibrillation of the heart".[3]

Later Wiener investigated the theory of the nerve spike by attempting to set up and solve the differential equations of impulse flow along the nerve. The statistical theory of the conduction of impulses through a synapse was also researched. In addition Wiener hoped that electroencephalograph patterns could be transformed into clear pictures "quite unlike the illegible confusion of the crude records"[2] by means of harmonic analysis. Cybernetics was his creation and Wiener set no limits to its application.

> There are two other fields where I ultimately hope to accomplish something practical with the aid of cybernetic ideas . . . One of these is the matter of prostheses for lost or paralyzed limbs . . . (The other is) the automatic factory, the assembly-line without human agents, (which) are only so far ahead of us as is limited by our willingness to put such a degree of effort into their engineering as was spent, for example, in the development of the technique of radar in the second world war.[3]

During the seventy years of his life Wiener published over two hundred scientific and philosophical papers and twelve books. In addition he received many awards from scientific societies throughout the world in recognition of his contributions to mathematics and neurophysiology. The future effects of the science of cybernetics, created by the efforts of one man's genius, cannot be estimated at this time. For example, one of his latest ideas was that crystalline nucleic acid complexes interacting in neurons each have specific spectrums of vibrations and form the basis of memory. Would it not be possible to use nucleic acid in computers to give a much higher information-storage bit index? Wiener's tempermant was always:

Couldn't this be so.[4]

B. N. French, B.Sc., 6T8

ACKNOWLEDGMENT

I wish to thank the librarians of the Medicine and Science Reference Room and my wife, Janice, for their help in the preparation of these articles.

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Special Review

Cybernetics, A Perspective

S. Gislason 6T7

The advent of electronic computation, and servomechanisms has precipitated a socio-economic revolution, currently en-route to a decisive metamorphosis of the contemporary life situation. The disciplines involved seek to further their impact on the course of history by direct application of their methodologies to the biological sciences, particularly in the analysis and description of human nervous system function.

Norbert Wiener crystallized a developing trend when in 1948 he first published, "Cybernetics, or Control and Communication in the Animal and the machine."[1] It was his intention, as he later stated in "The Human Use of Human Beings",[2] published in 1950, to gather together a heterogeneity of engineering and mathematical methodologies into a synthetic discipline, which he chose to call "Cybernetics" (from Greek roots, meaning "steersman"). He anticipated, thereby, a more coherent approach to the study of information and control, with special application to communication systems and human biology. Cybernetic methods offer the biologist a logico-mathematical system of concepts and operations, enhanced significantly by a repertoire of sophisticated machinery, and ask nothing in return but a rigorous mechanist's approach to soft-tissue phenomena, including the more abstruse manifestations of the human brain. As is true of any potent technology, there is much to be gained from the proper employment of Cybernetics, and much to be lost if misapprehensions and abuses prevail.

The discipline, Cybernetics, involves analysis (or creation) of systems from two points of view: 1) information, and 2) control. These points of view have achieved a practical realization in computer technology and the technology of automation respectively. Both points of view are usually two aspects of the same problem or the same phenomenon. Information seeks its dynamic feature, communication, and communicated information may be regarded in terms of its regulatory or control function.

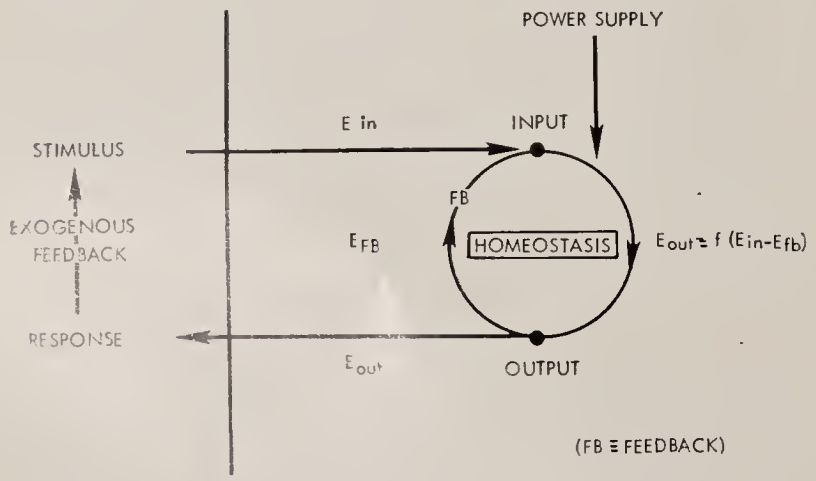

FIG. 1: A schematic closed-loop servomechanism.

Wiener compared biological homeostasis to the self-regulating activity of mechanical servomechanisms, and established the now-popular concept of feedback in the description of biological design. A *servomechanism* may be defined as any self-regulating device which controls a variable physical quantity (its OUTPUT), by comparing the effect of the output with a reference value (its INPUT) (Fig. 1). The difference between INPUT and OUTPUT is described as the *error signals*; and the servomechanism is arranged such that the error signal acts through an effector to minimize itself (i.e. to minimize the difference, OUTPUT — INPUT). A steady-state is achieved when, ideally, the error signal is zero; or practically, when the error signal reaches a small constant value.

The comparison of output to input is managed by a device called the "comparator" or the "compensator". The comparator is often the most sophisticated element of the system, since it may generate an error signal which is a function of the difference (OUTPUT—INPUT); this function may answer any mathematical description, often including compensatory features, which minimize discrepancies among the elements of the control system. The comparator receives a small recursive fraction of a sample of the output, which is termed the "feedback". The feedback acts in a negative way in a servomechanism—i.e. E_{FB} (Energy of Feedback) is subtracted from, or reduces E_{IN} (E input) so that $E_{OUT} = f (E_{IN} - E_{FB})$ (Fig. 2). The feedback signal may be of small magnitude with respect to the effector signal and/or the input signal; the comparator may act then as an amplifier and achieve *feedback-gain* in generating an error signal, just as a small grid current in a triode tube will regulate a larger cathode-anode current.

In information terms, the input of the system is a *command-signal*; the output an attempt to follow the command; and the feedback a measure of the difference between intended effect and actual effect. The thermostat (Fig. 2) serves as a common example of a comparator in a self-regulating system. The "set" of the thermostat is the command signal (i.e. the input or reference value), which is compared with the actual value of the output (as registered by a thermometer, or thermocouple); the difference INPUT-OUTPUT becomes the error signal (eg. set is 72°, actual temperature is 65°, magnitude of error is 7°), the thermostat acts to translate the error to an error signal which has a simple ON and OFF characteristic; the furnace is turned on and remains on until the feedback (the small fraction of the furnace's output which raises the thermometer reading) diminishes the error signal when the set

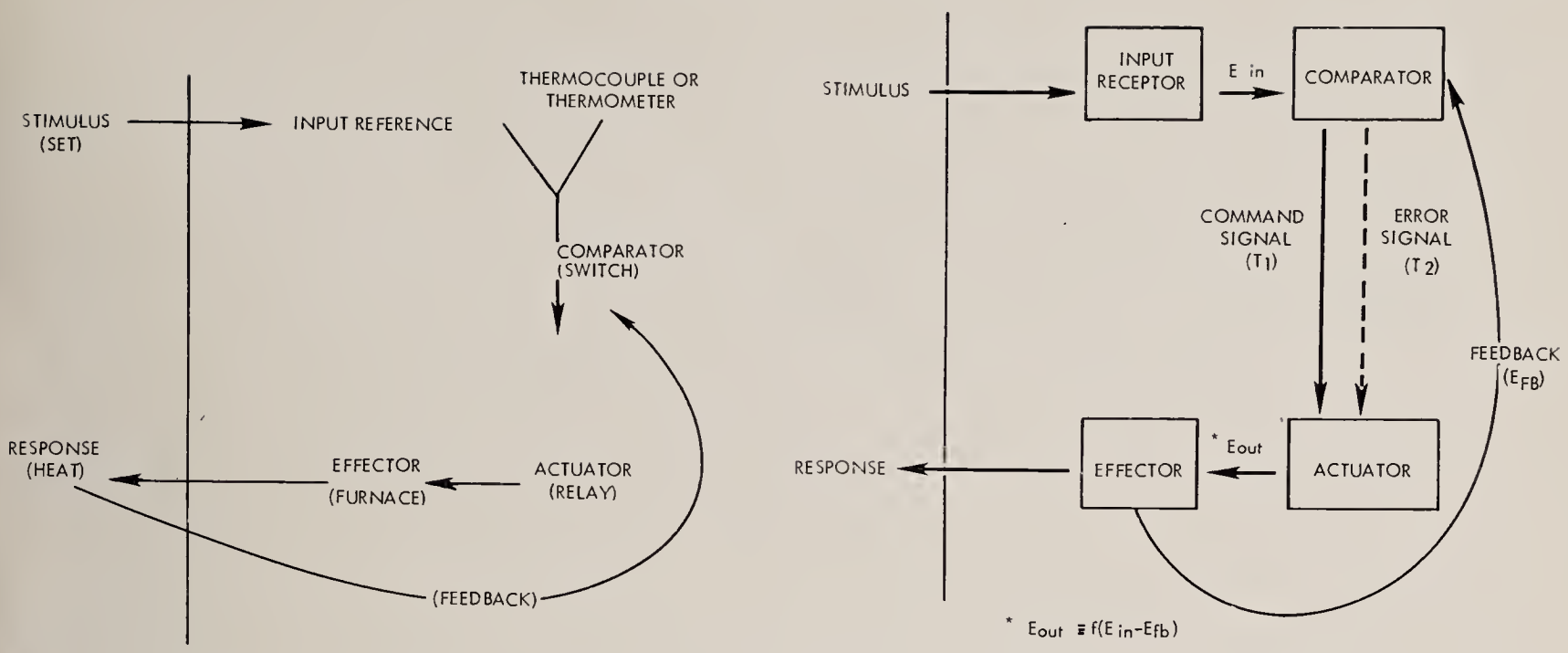

FIG. 2: Thermostat control (left) an example of a servo-mechanism with comparator (schematic representation on right)

and actual temperature become equivalent. The simplicity of this system is somewhat misleading since the variables involved are linear, the output has only two states, and the time-factor is not an independent variable (i.e. it is implicit in the error signal). The paradigm of the thermostatic control system is employed in the description of hormonal servomechanisms, and however oversimplified that concept may be, it does facilitate comprehension of neuro-endocrine function.

To illustrate a slightly more complex servomechanism, with the time factor as an independent variable, consider a hypothetical system with a continuous variable input and output. The output must be considered now as a continuous variable function of $(E_{IN} - E_{OUT})$; expressed mathematically in terms of summation and integral equations involving both linear and non-linear functions; however, further mathematic elaboration is beyond the scope of this article. The net result is that such a system is dependent on the appropriate phasing of output frequency response to the input frequency to maintain a negative feedback situation, and thereby, stability (i.e. the output "keeps-up-with" the input). Inappropriate phasing leads to break-down of the system with runaway situations or oscillation as the result. The comparator in the system has much to do with maintaining stability. It may, for example, involve an anticipatory error signal, should the output response be particularly sluggish; or the comparator may be designed to react not only to the difference $E_{IN} - E_{OUT}$, but also to the rate of change of this difference, thereby modulating the potentially catastrophic effect of a rapidly changing input signal. Most servomechanisms are a compromise between a system which is sluggish but stable, and one which is quick to respond but prone to oscillate. Most biological control systems are sluggish —or in electronic parlence, "highly-damped". Autonomic nerve fibres are, for example, usually non-myelinated, and transmit slowly; their homeostatic effectors (eg. smooth muscle) are comparatively slow to respond; certainly the hormonal feedback systems adopt a leisurely attitude to their regulatory function.

Let us view biological systems in general, very briefly, before regarding specific physiological examples of servomechanisms. A living system struggles continuously to maintain a transient enthalpic defiance of the entropic tendency of its universe. Energy is borrowed from the external milieu and routed through specific processes of energy transformation, which serve the self-referring ends of the organism—perpetuation of self and kind. This audacious living scheme requires an astute system of control interposed between stimulus and response, stress and adaptation, receptor and effector. The control is manifest as homeostasis, a condition synonymous with survival. The complex organism relies on a nervous system with hormonal support to achieve its homostatic ambitions. We may view the human nervous system as approaching its control functions on two levels: 1) the level of vegetative control, served by an elaborate com-

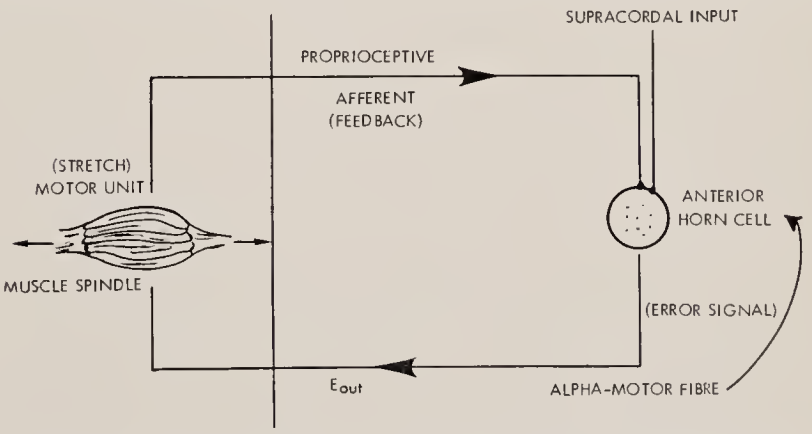

FIG. 3: The segmental reflex are as a servo mechanism. It is to be noted that the true input of this system arises from Supracordal Centres, specifically via the Cortico Spinal Tract. The Proprioceptive Afferent return, as feedback, continuously monitors the state of the effector (motor unit). It is an example of feedback being generated not by alteration in input state, but by an alteration of output or effector state, a common situation challenging Biological Servomechanisms.

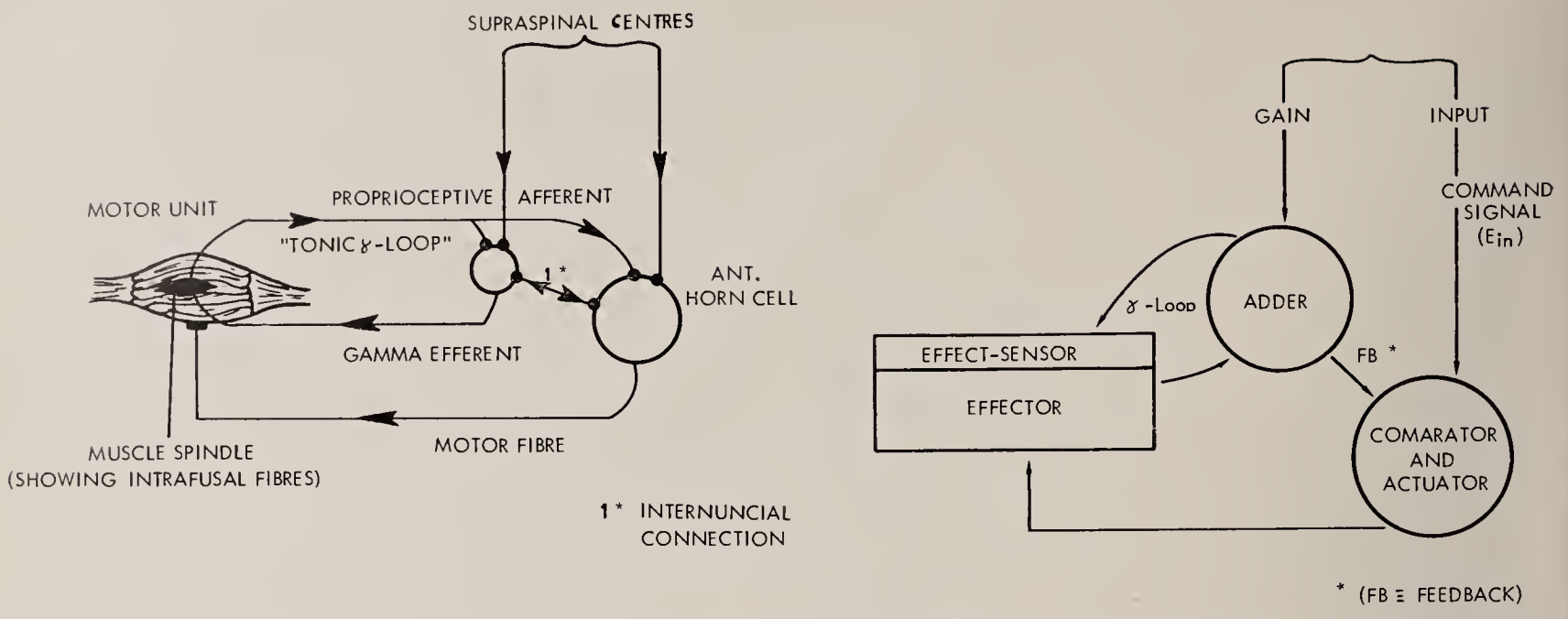

FIG. 4: The gamma-loop system (left) and its cybernetic schemata (right). Gain = the supraspinal control of gamma-neurons. Adder = gamma-neuron. Comparator and Actuator = alpha motor neuron. Effect-Sensor = muscle spindle. Command Signal = corticospinal action potentials.

plex of genetically determined patterns of function—the fruit of phylogenetic learning; and 2) the level(s) of higher control characterized by the use of information, acquired ontogenetically. The higher centres of the human brain have perhaps exceeded their fundamental biological responsibilities, in acquiring dimensions of activity out of phase with the ebb and flow of input and output. It is this unique evolutionary development of brain function which interests us most, and which is least accessible to cybernetic analysis. Our most reliable servomechanisms are found in the lower brain centres and spinal cord, and our least reliable servomechanisms operate through the cerebral cortex—indeed the higher centres of the human brain are characterized by unpredictability, perhaps most poignantly manifest in the wealth of irrational behaviour that men and rabid dogs seem to have in common. Most cyberneticians (and experimental psychologists, for that matter), would apparently rather ignore the occult and indeed the sublime aspects of human identity, in favour of the ostensibly rational and predictable aspects.

Let us regard briefly one of our reliable control systems: that of the reflex arc involving muscle spindles (Fig. 3). For the moment consider the circuit: Alpha-motor neuron and efferent axon, muscle-effector, proprioceptive transducer (muscle spindle), afferent axon, and central synapse with alpha-motor neuron. This circuit represents a closed-loop feedback control system, activated by passive-stretch of muscle fibres—the intrafusal fibres of the muscle spindle are concomitantly stretched, and generate an increased frequency of afferent action potentials (i.e. feedback signal). The motor neuron serves both as comparator and actuator—comparison occurs as integration of post-synaptic potentials on the membrane of the neuronal soma. If the sum of exitatory post-synaptic potentials reaches threshold, the neuron fires; the efferent action potential (the error signal) causes the muscle to contract, alleviating the stretch on the intrafusal fibres (i.e. the error signal acts to minimize itself), the proprioceptive feedback is decreased, and a steady state temporarily obtained.

This closed-looped system of segmental control may be considered as an open loop system with the addition of the gamma neurons, and gamma efferent fibres, under the control of supraspinal centres (Fig. 4). The gamma neurons may be considered as regulators of segmental feedback control, and a means by which higher centres may alter the "set" or "gain" of the reflex arc. The gamma loop comprises a gamma efferent axon, innervating the intrafusal fibres of the muscle spindle, and an afferent return of proprioceptive afferent collaterals to the gamma neuron. The gamma fibres are appropriately slow conducting with conduction-velocities of 20–40 metres/second (compared with alpha-motor fibres which conduct at 60–115 m./sec.). The gamma neuron receives input signals from supracordal centres, including the descending reticular inhibiting pathways, and from anterior horn cells; possibly from internuncial and other gamma neurons. An increase in the frequency of gamma efferent action potentials increases the gain of the segmental reflex arc and visa versa. (Fig. 4 renders the gamma-loop system in cybernetic terms.) Resting or postural muscle tone depends on the activity of the gamma loop. One might predict that if this control system oscillates, for any reason, a resting tremor ensues; or if the system is released from higher inhibitory control, the "gamma-gain" may increase to produce hypertonicity, indeed spasticity or rigidity of the muscles concerned.

It will suffice to briefly mention positive feedback in contrast to negative feedback. Positive feedback is of interest particularly as a description of confused, oscillating, or run-away control systems. Positive feedback

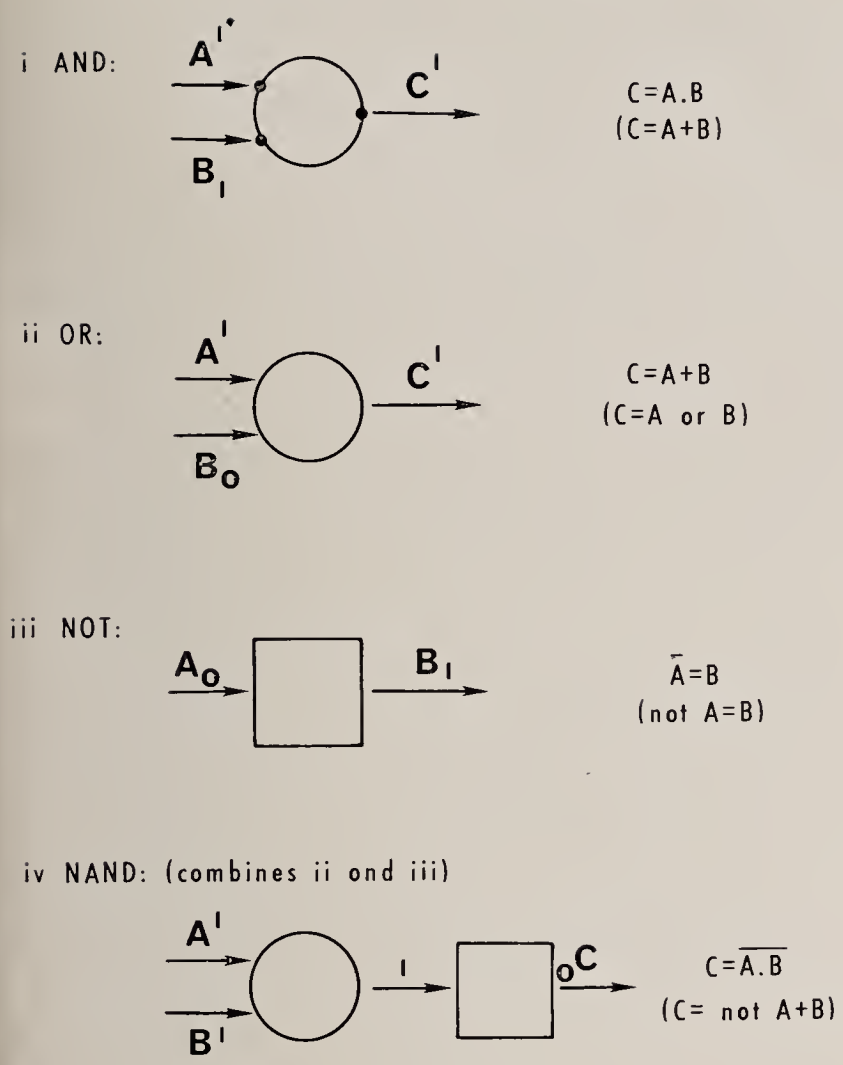

FIG. 5: Schematic binary logic elements.

obtains when the feedback signal is *added* to the input signal, so that the error signal is greater than the original input. An increase in the output signal of a system in response to a stimulus (input) will generate an enlarged error signal which in turn exaggerates the output —a vicious cycle is established. The initial stages of excitation of a nerve conductile membrane may be regarded as analagous to positive feedback; whereby, an excitatory post-synaptic potential decreases the transmembrane resting potential, increasing the sodium ion conductance; this in turn further depolarizes the membrane, again increasing sodium conductance; happily the cycle is not interminable, since at a threshold, depolarization the system explodes with the generation of an action potential.

This paradigm of positive feedback reminds us of many grosser situations of life, and perhaps this descriptive category may be uscd in the analysis of psychopathological states (eg. a stressful situation engenders anxiety with palpitations and hyperventilation; the sensory feedback from the visceral arousal aggravates the anxiety, compounding the physiological excitation . . . a run-away state ensucs.) In general terms, some of the manifestations of neurotic illness may be considered as aberrancy of control systems wherein both endogenous and exogenous feedbacks act in a positive manner, producing run-away or oscillating behavioural situations.

The application of cybernetic analysis to central nervous system function is at best difficult. The prerequisite data for direct analysis include 1) an input point; 2) an output point where an actuator or effector signal can be measured and regarded as a response to the input stimulus; and 3) an accessibility to the feedback loops involved, permitting precise manipulation of operating conditions. In other words, virtual isolation of the system is necessary for reliable analysis, and this condition cannot, as yet, be realized in the study of the human brain.

Theories based on analogies between mechanical servomechanisms, computors and biological systems are more easily obtained. Certainly hasty over-simplications, and naive mechanistic enthusiasms are to be condemned in this regard. Servomechanisms do exist in biological design, and their role is manifest in homeostasis, although as Schlesinger points out, "The maintainance of a steady-state is not the essence of life, but merely one of its prerequisites . . . the stability of living systems is maintained by controlled lability . . . paradoxically one of the functions of the higher organism is the production of dyshomeostatic states or goals which are superceded by the re-establishment of biological equilibrium often at higher levels of existence and experience . . ."[3]

Consideration of the information aspect of Cybernetics requires a rudimentary understanding of computation devices—those omnivorous calculating machines, whose cultural role as servant or master remains undecided. These machines employ a digital system of computation, based on binary logic. The basic unit of a digital system is a device which has two states (noted as O or I). The original unit was a relay (i.e. a simple mechanical switch with an ON and OFF position) subsequently replaced by diodes, transistors, and microcircuit elements. Each isolated unit handles one BIT of information (that is the binary decision O or I), and the computer builds numbers or characters through the combination of bits. The alphabet, for example, could be built from the combination of five bits (i.e. the combinations from OOOOO to IIIII; the number of combinations being 2^5). Usually the alphabet is represented by a 7-bit code, the extra combinations serving as notations for upper and lower case letters, spacing, punctuation, etc. Word-phrases or sentences are then translated into strings of seven-bit characters. Numbers are similarly represented. A given number is reduced to the base two (eg. $45 = 2^5+2^3+2^2+I$) and the powers of 2 are represented by a string of bits (eg. $0 = 0$, $10 = 2^1$, $100 = 2^2$, $1000 = 2^3$). An odd number is notated by 1 at the end of the string (i.e. $I = I$, $II = 2^1 + I$, $III = 2^2 + 2^1 + I$); 45 would be represented as, I0II0I.

Information, once processed, is subjected to the logical scrutiny of the computation device, whose operations

are determined by a program and by the circuitry of the machine. The basic logical operations on bits are binary (I.E. O or I, + or —) and circuits are designed to make judgments on the relationship of individual bits in a sequential manner employing one-bit temporary store circuits (flip flops). These circuits are arranged to express their output as a function of their input—if A and B are the two input variables and C the output variable, C is a decision about the relationship of A and B. For example, a circuit may judge concurrence of A and B—i.e. C = A and B, or equivalence, i.e. C = A or B, or contradiction B is equal to not A. If these logical sets are combined the circuit may judge C = not A and B ("NAND") or C = not A or B ("NOR"). These circuits act out logical syllogisms as might be expressed by Venn diagrams of set inclusion exclusion, or by Boolean statements (Fig. 5).

The contemporary transistor computer with sophisticated memory devices such as the magnetic—core which expresses the O or I decision in terms of the polarity of its magnetic field, can perform mammoth computation tasks in incredibly short periods of time. With the proliferation and sophistication of input and output hardware, and programming the range of tasks amen able to computer solution is ever expanding, and begins to involve intimate association of man and machine in creative technological endeavours; one facit of this association is the investigation, if not the encouragement, of computer intelligence. The qualities of computer operation which have been sought in recent imaginative studies are functional independence (teleology?), ability in abstract and analogical "thinking", and linguistic skill and learning. In essence, computer-intelligence is to be seriously regarded if a machine can acquire relative autonomy, characterized by conceptual-computation, and a progressive self-corroborating and self-correcting adaptation to changing problem situations. Although students of computer operation are enthusiastic about the potential of these machines to acquire this heuristic autonomy, their results to date are perhaps more a testimony to their own ingenuity than to anything else.

Quite early in the game, the analogy between the all-or-none function of the neuron and the on-and-off function of the computer unit (relay, diode, transistor) was made with the contingent speculation that the brain functioned much like a digital machine. The analogy has been elaborated in terms of the theory of finite automata—that neurons worked as binary units, and were arranged in neural nets or matrices which operate as logical nets—living representations of matrix algebra.

It is appropriate to conclude with a capitulation of concern about the possible abuse of cybernetics. Certainly Norbert Wiener was himself concerned with the socio-economic influence of industrial automation, and indeed with the growing cult of "gadget worshippers".[4] Wiener has written,

"Pere Dubarle has called the attention of the scientist to the growing military and political mechanization of the world as a great superhuman apparatus working on cybernetic principles. In order to avoid the manifold dangers of this, both external and internal, he is quite right in his emphasis on the need for anthropologist and philosopher. In other words, we must know as scientists what man's nature is and what his built-in purposes are, even when we must yield this knowledge as soldiers and statesmen; and we must know why we wish to control him.

". . . I have said that the modern man, and especially the modern American, however much 'know-how' he may have, has very little 'know-what'."[5]

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Clinicopathological Conference

Pyrexia, Weight Loss And Abdominal Pain In An Elderly Man

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W. S. Tucker 6T8

G. L., a 61-year-old stockbroker, complained of left flank abdominal pain of three months duration. An intravenous pyelogram performed at the time suggested an abnormality in the upper left urinary tract. He was admitted to the Toronto General Hospital for further investigation.

He had been well until three months prior to admission when he developed an influenza-like condition with rhinitis, sore throat, and a dull, fluctuating, periumbilical pain associated with intermittent fever. The pain shifted to the left flank where it intensified and became persistent. For two months previously, he had noticed anorexia, lack of energy, and had lost twenty pounds. There had been no nausea, vomiting, dysphagia, change in bowel habits, melena, or history of previous abdominal pain. He had never suffered from urological symptoms. He had smoked two packages of cigarettes a day for many years but had no history of chest complaints; however, for a three-week period before admission he had been coughing up an ounce of blood-tinged sputum each day. There were no symptoms referrable to the nervous system at this time.

As a child he had scarlet fever. At age 25 he suffered an episode of rheumatic fever, but there were no serious sequelae. More recently he had a hemorrhoidectomy and an inguinal herniorrhapy. Until three years before admission, he had consumed three to four bottles of whiskey per week for twenty years. After several unexplained episodes of loss of consciousness, he stopped drinking.

Physical examination revealed a well-developed, somewhat flabby, male who showed some signs of recent weight loss. The pupils were very small but equal in size, and reactive to light and accommodation. A cataract was noted in the right lens. On fundoscopic examination, minor arteriosclerotic changes were noted. The chest was clear except for rhonchi in the left lower lobe posteriorly. The pulse was regular at 72/minute, the supine blood pressure was 110/80. No masses were palpable in the abdomen. The prostate was slightly enlarged and non-tender to digital palpation. No lymphadenopathy was found. Neurological examination was normal.

Radiological investigation included chest films, upper and lower G.I. examination, retrograde pyelogram, and a voiding cystogram. Retroperitoneal air insufflation studies and aortography were not done. A voiding cystogram showed no ureteral reflux, a normal bladder, and the retention of 85 ml. of dye within the bladder after voiding. On cystoscopic examination, 120 ml. of residual urine and a slightly enlarged prostrate gland were the significant findings. A left-sided retrograde pyelogram showed obstruction at the uretero-pelvic junction and retention of dye within the dilated kidney pelvis well past five minutes. The left calyces and pelves were distorted and effaced. The left upper pole could not be delineated, so nothing could be said about overall renal size or displacement. The lower pole calyces were distorted by what appeared to be a mass expanding the parenchyma. It was felt that the renal effacement was due to an adjacent mass, rather than an intrinsic tumour.

Chest films revealed a normal heart shadow and bony structure. A fairly discrete, rounded density was present in the posterior part of the right lower lobe. No other discrete nodules were seen in either lung, but there was peribronchial fibrous tissue thickening around both hilar regions, suggestive of chronic inflammatory change. There was also some suggestion of calcification in the right hilum, although this was partly obscured by calcified costochondral cartilage. Both lung roots were

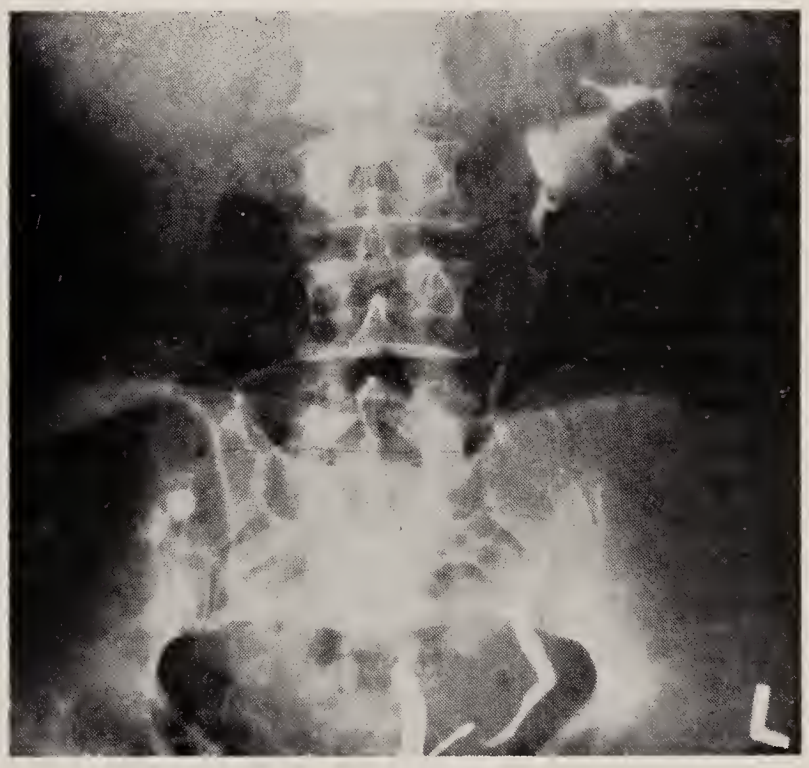

FIG. 1: Retrograde Pyelogram of Left Kidney.
Distorted pelvis and calyces are associated with a tortuous, partially dilated ureter. An incidental finding is two calcified mesenteric nodes in the right lower quadrant.

FIG. 2: Admission Chest X-Ray.
The important features are hilar enlargement, probably caused by hilar lymph adenopathy and dilated pulmonary arteries, and a circumscribed nodule in the right lower lung field.

enlarged, particularly the left, the appearance being suggestive of lymph node enlargement. However, part of the multinodular appearance was thought to be due to enlarged pulmonary vessels. These blood vessels were much more prominent in the medial parts of the lung fields, whereas the peripheral vessels were smaller and more tortuous. One large emphysematous bulla was evident in the left lower lobe. There was also a localized elevation of the medial part of the left hemidiaphragm. The entire picture was compatible with metastatic carcinoma; however, a granulomatous process such as tuberculosis or sarcoidosis could not be ruled out.

An upper gastro-intestinal series was normal. The colon, on barium enema examination, was greatly enlarged and had three times the normal amount of barium in it. Calcified mesenteric lymph nodes were found incidentally on this examination. No electrocardiographic abnormalities were demonstrated. The hemoglobin was 8.6 gm. %, the ESR 120 mm/hr. The blood film displayed mild anisocytosis, some polychromasia, and macrocytosis. Platelets appeared normal. The white blood cell count was 9,600/cmm composed of neutrophils 79%, eosinophils 3%, lymphocytes 13%, monocytes 8%. A direct eosinophil count yielded 331 cells/mm.^{3} The reticulo-cycle count was 2.2%. A random urine sample had a specific gravity of 1.012, a pH of 7.0, and no ketones, sugar, protein, or blood. A twenty-four hour urine collection of 2330 cc. had 11.5 mgm/24 hr. of 17-ketosteroids (normal: 10-11 mgm), and 4.8 mgm/24 hr. of 17-hydroxysteroide (1-10 mgm). A mid-stream urine culture grew less than 1,000 staphlycocci colonies. There were no acid fast bacilli on three separate sputa. An old tuberculin test on the forearm (1 T.U. in 0.1 ml. normal saline) was negative after three days. The blood sugar was 64 mg%, the BUN 9 mg%, serum sodium 132 mEq/L, potassium 5.4 mEq/L, and Co_2 content 22 mEq/L. Serum alkaline phosphatase was 34 I.U. (normal 15-50 I.U.), serum acid phosphatase was 9 I.U. (5-15 I.U. is normal), and the prostatic acid phosphatase was 2 I.U. (1-5 I.U. is normal). A sternal marrow puncture showed no abnormality of the hematopoietic cells and no malignant cells. As the hemoglobin was still 9.0gm%, the patient was given 4 units of whole blood and a laparotomy was performed.

THE OPERATION

On the eleventh hospital day, an operation was performed. Four benign cysts were discovered in the left kidney. The largest one, located upon the antero-medial surface, contained 300 ml. of blood-tinged fluid. A firm mass at the upper pole was removed for biopsy. This retroperitoneal structure weighed 117 gm. and was unattached to the spleen, liver, or stomach. It was not directly invading the renal parenchyma, but seemed to be displacing the kidney downward. Upon further dissection, the mass was seen to be intimately involved with the left adrenal gland. Other masses were palpated in the region of the coeliac axis and the periaortic area.

POSTOPERATIVE COURSE

On the fourteenth hospital day (three days postoperatively), the patient was alert, responsive, and in no apparent distress; however, it was evident that he had lost still more weight (a total now of 30 lb.). The chest was hyper-resonant except for dullnes at the left base. There was an increased expiratory phase with rhonchi, rales, and poor basal air entry. The pulse was 80 per minute, the blood pressure 140/70. The first sound at the mitral area was split and no murmurs were heard. The liver was palpated below the right costal margin. It was non-tender, smooth, and had a sharp edge. No lymphadenopathy was present. There was limited lateral gaze in the right eye. The muscular power and tone were normal. Reflexes were 2 + bilaterally; the plantar responses were downgoing. Pain, position, and vibration were well perceived.

Postoperatively the serum sodium levels averaged 130 mEq/L, potassium 4.8 mEq/L, chloride 97 mEq/L and Co_2 content 25 mEq/L. The blood sugar was 111 mg%, the BUN 27 mg%. Hemoglobin was 10.9gm%. Macrocytosis was seen on the blood film. No malignant cells were found in the sputum on three separate occasions. Repeated searches for acid-fast bacilli were also negative. Serum protein was 5.9 gm%, alubumin 2.7 gm% and globulins 3.2 gm%. Electrophoretically, of the globulins, alpha-1 was 8% (normal 3-6%), alpha-2 12% (6-11%), beta 12% (8-14%), and gamma 26% (10-22%).

A skeletal survey taken revealed minor degenerative disc changes in the neck, but no metastatic disease.

On the nineteenth hospital day (eight days postoperatively) he had opthalmoplegia and right facial weakness. The patient reported that he had first noticed double vision while watching television two days previously. He had no complaints with respect to his limbs but now admitted to an intermittent pain in the right temporomandibular joint for the past six weeks. Detailed neurological examination revealed a drowsy, but easily aroused, male who was well-orientated and co-operative. His intelligence seemed unimpaired. The visual fields were full to confrontation but fundoscopic examination could not be carried out due to the very small pupils. He was unable to voluntarily adduct or abduct the right eye, or adduct the left eye. Both eyes adducted minimally on convergence, but no voluntary, reflex, or following movements could be elicited in the direction of paralyzed gaze. Vertical axis movements, in contrast, were normal bilaterally. No nystagmus was detected. He had a crossed diplopia on left lateral gaze. Both pupils reacted to light, but their small size made it difficult to be sure that they constricted upon accommodation. An inability to close the right eye had led to excessive lacrimation. The patient noted a decrease in sensation in the right cornea, and along the distribution of the mandibular branch of the right trigeminal nerve. There was a right-sided facial weakness, which affected the lower part of the face more than the upper; although usually signifying an upper motor neuron lesion, this was taken to be an almost complete, peripheral, seventh nerve lesion. The eighth to twelfth cranial nerves were normal. The muscles appeared normal in power, bulk, and tone: a slight intention tremor in both arms was attributed to a weakened state. Coordination was normal in the lower limbs. The reflexes were unchanged from the previous examination and no Hoffman's sign was present. Below the neck sensation was intact to all modalities. Speech was unimpaired.

Prednisone administration was begun on the twentieth hospital day in the hope of reducing brain-stem edema. The right eye, which had become inflamed, was covered. The progressive deterioration of the patient's state of consciousness, as well as the development of ophthalmoplegia were considered indications for pontine irradiation; therefore, 2,000 rads were given to the left lateral skull field, and 1,800 rads to the right lateral skull field, over a period of nine days in progressively increasing fractional doses. The patient was given demerol.

No objective improvement resulted. On the twenty-seventh hospital day the patient could no longer walk. He fell to the left side and complained of weakness in the left arm and left leg.

The sputum was negative for malignant cells and acid-fast bacilli on four more occasions. The serum sodium was 133 mEq/L, potassium, 5.3 mEq/L, chloride 93 mEq/L, CO_2 combining power 27 mEq/L, calcium 9.8 mEq/L, phosphorus 3.1 m/EqL; the BUN rose to 51 mgm%. The blood sugar (2 hour post-prandial), was 110 mg%.

On the thirty-first hospital day, the weakness had progressed such that the patient was unable to lift his left arm. The next day he was very drowsy, but his reasoning remained clear. The left arm could not be moved at all. He could not wiggle the toes on his left foot. The biceps was ++ on the right, and negative on the left. Patellar reflexes were ++ bilaterally. The plantar was much more downgoing on the left. Vibration sensation was intact bilaterally, but position sense was decreased on the left. He gradually fell deeper and deeper into unconsciousness, and became completely paralyzed in his left leg. The progressive loss of consciousness led to his death on the thirty-fourth hospital day.

DIFFERENTIAL DIAGNOSIS

With the history of abdominal mass, weight loss and neurological signs, it is most probably that this patient has a malignant neoplasm. Two areas are likely to be the source of the primary tumour.

1. Chest—right lower lobe.

The most probable cause of a single lesion in the right lower lobe of this patient, associated with hilar enlargement and weight loss, and the couhing of blood-tinged sputum for three to four weeks prior to admission, is *bronchogenic carcinoma.* The left flank pain and pyelographic evidence of an extrinsic mass adjacent to the left kidney might well indicate metastatic spread which, in the case of bronchogenic carcinoma, is particularly likely to involve the adrenal gland. It is difficult to explain the colonic dilatation on the basis of bronchogenic carcinoma, in the absence of a constricting lesion distally, but this finding is difficult to explain with any of the information given here. The pulmonary findings could also be due to secondary spread to the lung of tumour from the colon, the left abdomen, or other sites not implicated by investigation. However, secondary tumour is usually found in multiple sites in lung. This would be especially likely if hilar involvement also exists in the secondary malignant process of extrapulmonary origin. The chest findings could possibly be unrelated to the mass and could be due to a *healed tuberculous nodule, sarcoid,* or various fungal infections which occasionally give solitary masses or abscesses in lung, *bronchial adenoma,* which is a relatively rare tumour, and occurs in a younger age group, but is often associated with hemoptysis.

2. The structures lying in the left side of the abdomen.

The findings in the left abdomen could be due to disease of the kidney, adrenal, colon, stomach, pancreas, or several of these organs.

The kidney is an unlikely site of the primary disease, because of the absence of specific urinary tract

symptoms, especially hematuria, and the radiologist's impression that the abnormality of the pyelogram was due to an extrarenal mass. Nevertheless, one cannot rule out *hypernephroma*, which often presents with flank pain, and which frequently metastasises to lung. *Single renal cysts* occur quite commonly, but a diagnosis of isolated renal cyst would not explain the other findings.

Adrenal cortical tumours may be malignant or benign-and these can be functional or non-functional. There is no evidence of an increased adrenal cortical function in this patient, associated with overproduction of glucocorticoid, aldosterone, androgen, estrogen, or any combination of these hormonal substances. The patient was normotensive, and electrolyte studies suggested, if anything, aldosterone insufficiency. (Serum No. 130 mEq/1., K 5.5 mEq/1., Cl 100 mEq/1., CO_2 content 22 mEq/1.) There was an absolute eosinophilia (331/mm.^{3}, compared with a normal value of 50-200/mm.^{3}), suggestive of some glucocorticoid insufficiency. Urinary 17-ketosteroids were normal, as were urinary 17-hydroxysteroids. Though these data largely negate a functional adrenal corical tumour, the apparent insufficiency supports some involvement of the adrenal cortex, either by non-functioning primary or secondary tumour.

Adrenal pheochromocytoma is the commonest primary tumour of the adrenal medulla. Of these, only about 13% are malignant. Further, this patient had no history of hypertension, either intermittent or persistent, diarrhea or excessive sweating. He did not exhibit diabetes or a hypermetabolic state, which are commonly associated with the atypical pheochromocytomas which secrete predominantly epinephrene, and produce the so-called "metabolic syndrome". Other *tumours, sympathogonioma, ganglioneuroma*, and *neuroblastoma* occur in children, and are very rare.

Carcinoma of the splenic flexure of the colon is quite unlikely in this patient. These tumours are usually of the annular constricting type, and give proximal distension and obstruction of the colon, with alternate constipation and diarrhaea, and often mucous and blood are passed per rectum. This patient has none of these findings, and his colon was dilated both proximal and distal to the splenic flexure.

Pancreatic tumour is unlikely. However, disease of the tail of the pancreas, tumour or cyst, could give this picture. *Carcinoma of the stomach* is an improbable diagnosis. There is no history of fullness, pain associated with eating, obstruction, or vomiting of altered blood.

NEUROLOGICAL FINDINGS

The progressive neurological picture is highly suggestive of a secondary intracranial tumour. The first indication of nervous system involvement was the loss of lateral gaze in the right eye, indicating a right sixth nerve palsy. This is generally considered to be a very non-specific finding due to pressure on the long intracranial course of the abducens nerve. The patient's report of right tempero-mandibular joint pain and facial anaesthesia even earlier, indicates involvement of the right fifth nerve, or its brain stem pathways. Next, right facial weakness developed, indicating involvement of the right seventh nerve. Eventually the patient was unable to close his right eye. Considered with the other features of this developing picture, this points to a lesion of the intra- or extramedullary sites, on the basis of carcinomatous deposit in brain parenchyma or the overlying subarachnoid space. The patient's ophthalmoplegia gradually became more extensive. Vertical movements were preserved in both eyes, while lateral movements were abnormal bilaterally. These findings rule out a complete third nerve palsy in either eye, as does the presence of small pupils, and support the diagnosis of an internuclear ophthalmoplefiia. The bilaterally small pupils may represent irritative effects of expanding tumour on the nuclei of Edinger-Westphal. (The patient was not receiving morphine. The patient had noted diplopia, and conjugate lateral gaze was paralyzed to the right and left. This paralysis was complete to the right, with no voluntary, reflex, or following movements. (In supranuclear lesions, anywhere between cortical areas in the middle frontal gyrus or near the visual area of the occipital lobe, and the contralateral sixth nerve nucleus, voluntary lateral gaze may be lost, with preservation of conjugate lateral deviation on following a finger).

A complete paralysis of conjugate lateral gaze is most often associated with pontine lesions, especially neoplasms. Crossed diplopia on left lateral gaze is indicative of a partial paralysis of the mechanism of conjugate lateral deviation. An intention tremor may have been the result of weakness, or metastases to the cerebellum or its brain stem connections, or other sites.

The patient's progressive drowsiness, and eventual unconsciousness may have resulted from neoplasm involving the reticular activating system of the brain stem, or from other sites of intracranial tumour, exerting their effect by raising intracranial pressure. Intellectual function was well preserved until coma supervened. The slowly progressive development of unconsciousness was apparently not modified by steroid therapy. The absence of gradually increasing headache largely negates increased intracranial pressure as the cause of the coma. Papilloedema could not be assessed, because of bilateral pupillary constriction. Furthermore, cranial nerve abnormalities point to a brain stem lesion, which can also explain the development of drowsiness, stupor, coma, and death. A left hemiplegia developed late in the hospital course. Because most of the other signs have pointed to right-sided pathology in the brain stem, we shall postulate involvement of the corticospinal tract from the right hemisphere to the left side of the body, perhaps at the pontine level. Thus we feel that the neuropathology in this patient was caused by secondary tumour, and that the likely sites of metastases are the

brain stem, predominantly the pons, perhaps the cerebellum or its brain stem connections, and perhaps higher portions of the brain.

Until recently, brain stem metastases were considered to be exceedingly rare. However, K. M. F. Hunter and N. B. Rewcastle have reported brain stem secondaries in 11.7% of 393 autopsies with intracranial metastatic tumour. The commonest tumours of origin in brain stem metastases, according to their paper, are, in order of frequency, lung, breast, melanocarcinoma, and kidney. The pons was most often implicated, with brainstem less commonly, and medulla least often. Frequently the diagnosis was not entertained because findings were ignored, in the belief that such metastatic spread was exceedingly rare or non-existant. The commoner clinical manifestations of these lesions include: progression of signs; hemiparesis; cranial nerve palsies, involving nerves three through seven, and the mechanism of conjugate lateral deviation; ataxia; hemisensory loss; and obstructive hydrocephalus.

PATHOLOGICAL DISCUSSION

A yellow-white, hemorrhagic, irregularly-shaped mass had been removed from the upper pole of the left kidney at operation. The diagnosis of a poorly-differentiated adenocarcinoma of the adrenal cortex was made on the basis of the histological appearance and the mass's intimate involvement with the left adrenal gland. This malignant, anaplastic tumour had large, pleomorphic, plump cells which grew in nests and cords separated by areas of extensive necrosis. The right adrenal gland weighed 85.0 gm., and was enlarged because of the presence of partially necrotic, variegated, yellow-white, hemorrhagic tumour tissue. A tiny remnant of normal cortex was discovered at one pole. This patient actually suffered from moderate adrenocortical insufficiency because of malignant replacement of the normally-functioning tissue of both glands. This was considered to be non-functioning adrenal carcinoma.

This tumour metastasized quite extensively. The peripancreatic, para-aortic, mediastinal, and hilar nodes were involved secondarily. Both kidneys had several small, necrotic metastases measuring up to 5 mm. in maximal diameter. Presumably the renal secondaries originated via retrograde lymphatic flow secondary to obstructed flow in the cysterna chyli-thoracic duct system. Alternate explanations might include hematogenous dissemination via the adrenal veins or via the thoracic duct into the right subclavian vein, or else by direct extension; however the diffuseness of the involvement and the lack of direct contact between the adrenal tumour and the renal tumours both weigh against the latter explanation. The lesser curvature of the stomach possessed one ulcerated (secondary) tumour (1.1 cm. in diameter), grossly indistinguishable from a gastric ulcer. Many umbilicated, ulcerated nodules were found mucosally, submucosally, and subserosally throughout the length of the jejunum. Extra-intestinal, malignant tumours have very little tendency to spread to the small bowel as a site of secondary deposit in any of the reported cases of adrenal carcinoma. Here the mechanism of spread could be transperitoneal as the jejunum is found predominantly in the left upper quadrant, the site of the primary tumour. It is more likely, however, that the mode of spread is retrograde lymphatic flow due to extensive lymph node blockage.

Despite the negative old-tuberculin skin test, and the absence of acid-fast bacilli on repeated sputum examinations, the patient proved to have healed, primary tuberculosis. The circumscribed nodule seen on the chest films and interpreted to be metastatic disease turned out to be a calcified, tuberculous granuloma, 5 cm. in diameter, in the apical segment of the right lower lobe. Calcified nodes were also present in the right hilum. Surprisingly, there was no metastatic disease in the lung parenchyma. Both lungs were congested and oedematous, and both bullous, centrilobular emphysema throughout their upper lobes. The right and left lower lobes both had recent infarcts. No reason was found for the increased pulmonary vasculature seen on X-ray; as well the source of an embolus to account for a recent infarct in the left kidney could not be determined.

The renal abnormalities displayed on retrograde pyelography can be explained by a combination of the adrenal tumour displacing and effacing from above, and the renal cysts the largest of which was 8 cm. in diameter, displacing laterally.

NEUROPATHOLOGICAL DISCUSSION

In examining the brain the answers to two questions were sought: what caused the drowsiness and progressive loss of consciousness, and what caused the focal neurological signs? The clinical impression had been intracranial metastases, including a pontine metastasis, while a vascular lesion could not be excluded. The cerebral vasculature exhibited only moderate atherosclerosis. On the right superior, frontal lobe was a hard, hemorrhagic area measuring 4 cm. by 2 cm. This proved to be a tumour deposit with pleomorphic nuclei and varying amounts of eosinophilic cytoplasm. Hemorrhage extended from the junction of the gray and white matter into the overlying subarachnoid space. The surrounding white matter exhibited chronic edema with scattered, hypertrophied astrocytes and separation of the myelinated fibres. Similar hemorrhagic metastases, up to 2 cm. in diameter, with surrounding edema, were placed in both parietal lobes, and in the left occipital lobe; these also had caused small subarachnoid hemorrhages. The right cerebral hemisphere had moderately flattened gyri. Both hippocampal unci were moderately notched, but not enough to affect the oculomotor nerves or the basis pedunculi. There was slight herniation of the cerebellar tonsils into the foramen magnum. Thus we can postulate some degree of increased intracranial pressure caused by

the expanding, hemorrhagic, edematous tumour nodules, and subarachnoid hemorrhage. It is unlikely that either the hippocampal or the cerebellar herniation were severe enough to cause a significant pressure upon, and circulatory embarrassment of the brain stem; thus the progressive drowsiness observed must be attributed to other lesions.

It is remarkable that the patient's mental faculties persisted as long as they did, and did not decrease as much as his level of consciousness did. Although these metastases were focal, the resultant effect of local hemorrhage and cerebral edema and flattened gyri be expected to depress reasoning, calculation, or cause some kind of aphasia.

One would be hard put to explain the bilateral intention tremor on either cerebellar coning (i.e. cerebellar tonsillar herniation), or the discrete, metastasis in the left cerebellar hemisphere. Other cerebellar signs such as ataxia, dysdiadokinesis, and nystagmus were lacking; therefore, one might question the presence of cerebellar dysfunction.

The brain stem contained a large, irregular, hemorrhagic tumour deposit situated in the tegmentum of the pons and extending 2 cm. from its caudal end to the caudal end of the mibrain. In its greatest width, this neoplastic focus measured 1 cm. The lesion was maximal in size at the level of the exit of the fifth cranial nerve; at this point it was located predominantly on the right side of the pons, but had destroyed the midline medial longtitudinal fasciculi on both sides. At this point it ruptured through the floor of the fourth ventricle. Hemorrhage and edema surrounded the tumour, and was particularly prominent in the right side of the right tegmentum.

Many neurological signs are explained by the tumour and the surrounding area of hemorrhage and edema. Both medial longtitudinal fasciculi were destroyed by tumour. Thus fibres from the contra-lateral region controlling lateral conjugate gaze and also fibres from the ipsilateral vestibular nucleus were affected. This explains the loss of reflex and following movement in the horizontal plane. The nucleus of the right abducens nerve in the caudal pons was also involved by tumour and hemorrhage; therefore, the right eye could not be voluntarily moved to the right in the horizontal plane. A crossed lateral diploplia upon looking to the left implies an intact abducens nerve on the left side: no abnormality was noted in the left abducens nucleus. Hemorrhage is known to irritate cranial nerve nuclei: the small, pinpoint pupils were caused by the midbrain hemorrhage irritating the parasympathetic third nerve nuclei. Hemorrhage and edema in that part of the oculomotor nucleus which controls the right medial rectus muscle will account for inability to adduct the right eye. As vertical movements were intact bilaterally the rest of the third and fourth nuclei must have escaped the effects of the edema. Similarly, differential edematous involvement of the main sensory nucleus of the right fifth nerve (touch), and part of the nucleus of the spinal tract of the right fifth nerve (pain and temperature) caused the facial sensory disturbances. The right facial hemiparesis was a combination of upper and lower motor dysfunction. Part of the right facial nerve (the genu) was destroyed by tumour as it swung medially around the abducens nucleus, and the facial nerve nucleus itself was edematous, as were the supranuclear or upper motor neuron fibres which make up the pre-synaptic fibres; for this reason, both upper and lower motor weakness is present. Edema may have impaired conduction within the descending pyramidal tract fibres within the right brachium pontis. Thus paresis of the left arm and leg slowly developed. The absent left biceps reflex may be attributed to early flaccidity found in upper motor neuron lesions, although this cannot be easily reconciled with the positive left patellar reflex. Edema of the right medial lemniscus accounts for decreased position sense in the left limbs. Again a differential effect is present because vibration, which also travels with the medial lemniscus, was intact. Finally, the tegmental tumour, with its hemorrhage and edema, destroyed the reticular nuclei and their afferent and efferent connections. This reticular activating system is responsible for maintaining consciousness and is therefore called the waking centre. Destruction of the waking centre causes loss of consciousness. Since thought processes such as calculation, memory, and judgment are not mediated by the reticular formation, they were maintained while the patient became progressively drowsier. As previously implied, the increased intra-cranial pressure may have had some effect as well.

CARCINOMA OF THE ADRENAL CORTEX WITHOUT ENDOCRINE EFFECTS

In 1957, Wood *et al.*[1] published a review of thirty-five cases of non-functioning adrenocortical carcinoma. The tumour was equally common in both sexes, and the age range was 17–73 years, the average age being 52 years. The left adrenal gland was the primary site in twenty-three cases, the right in ten, and one was not stated. *Loin* (i.e. flank) *pain* on the affected side, *intermittent fever* and *weight loss* were the three most common presenting symptoms. G.L. was thus a classical patient, for his tumour was on the left side and he had all three symptoms. The pyrexia was attributed to tumour necrosis since one patient became apyrexic when the tumour mass was removed (Cawdias). The pain was thought to be caused by necrosis and hemorrhage as well as by the bulk of tumour displacing and distorting the kindney (Griffiths). A palpable mass was present in 31% of cases. While plain film and intravenous pyelography were useful tools, the full extent of this highly vascularized tumour could be appreciated by aortography. The I.V.P. diagnosis is indirect and de-

pends upon the non-visualized adrenal gland displacing the visualized kidney. Prognosis was poor because the left flank pain, fever, and weight loss are the only clinical guides to diagnosis, and when all three are present, the tumour is usually too far advanced for anything except palliative surgery. In contradistinction, a functioning adrenal tumour makes itself evident earlier by certain various syndromes of hormonal excess: this in turn leads to earlier recognition and surgical intervention.

ANATOMICAL DIAGNOSIS

1. Carcinoma of the adrenal cortex, nonfunctioning, anaplastic.
2. Adrenalectomy left.
3. Metastatic carcinoma of lymph nodes, kidneys, right adrenal gland, G.I. tract, brain.
4. Hemorrhage and edema of pontine tegmentum, secondary to metastasis.
5. Primary pulmonary tuberculosis, healed, calcified, right lower lobe.
6. Pulmonary infarcts (2), lower lobes, bilateral.
7. Herniations a) hippocampal unci—moderate
   b) cerebellar tonsils—slight
8. (Internuclear Ophlhalmoplegia.)

ACKNOWLEDGEMENT

The authors gratefully acknowledge the generous assistance given to prepare this article by Dr. N. B. Rewcastle, of the Dept. of Neuropathology; Dr. Reilly, of the Dept. of Radiology of the Toronto General Hospital; Dr. K. M. F. Hunter, presently resident in Neurosurgery at Sunnybrook Hospital; Mr. D. Dunn, of the Photography Dept. of Princess Margaret Hospital.

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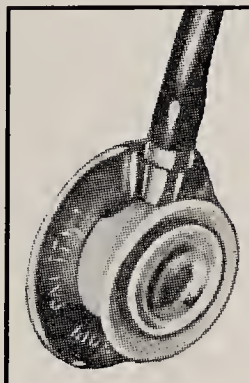

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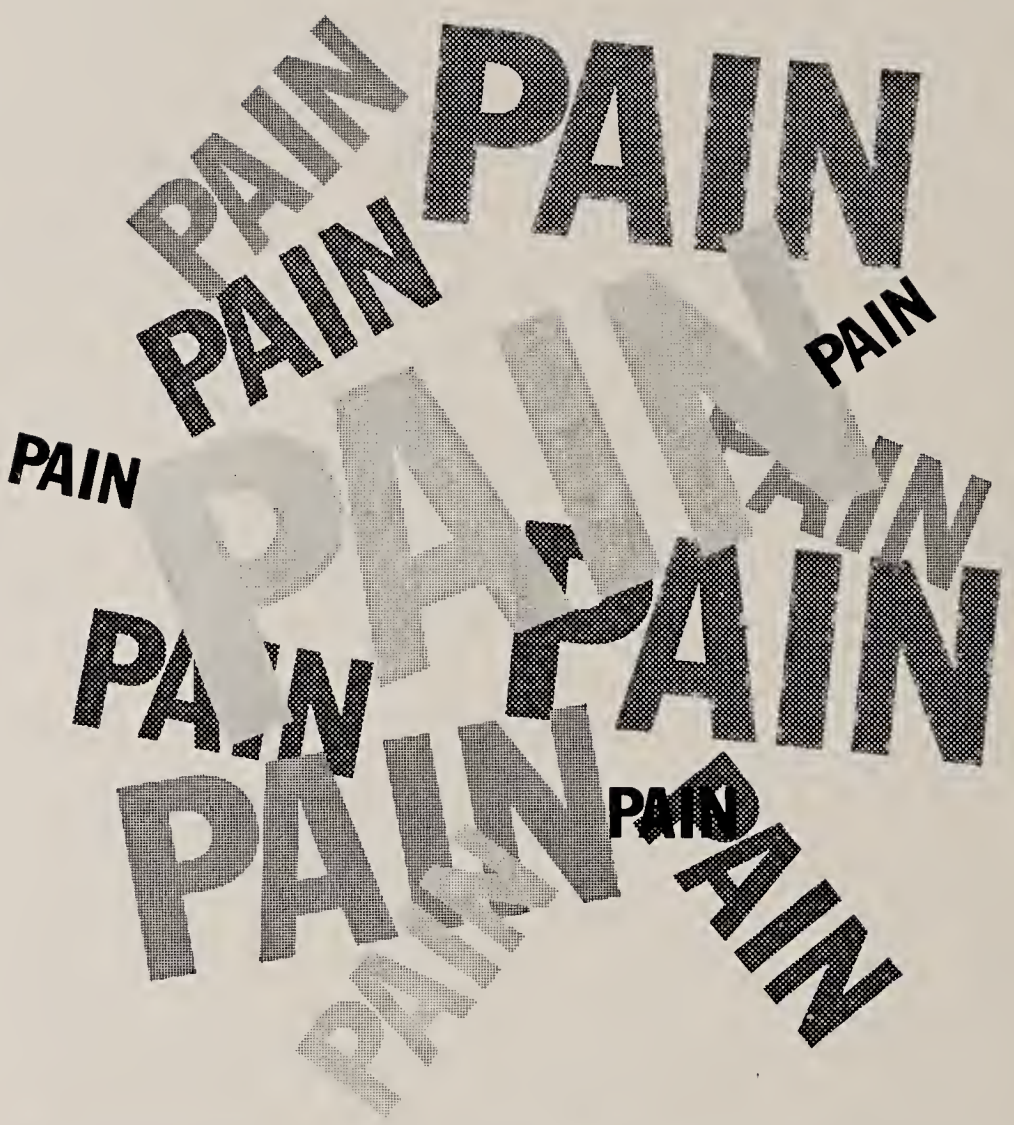

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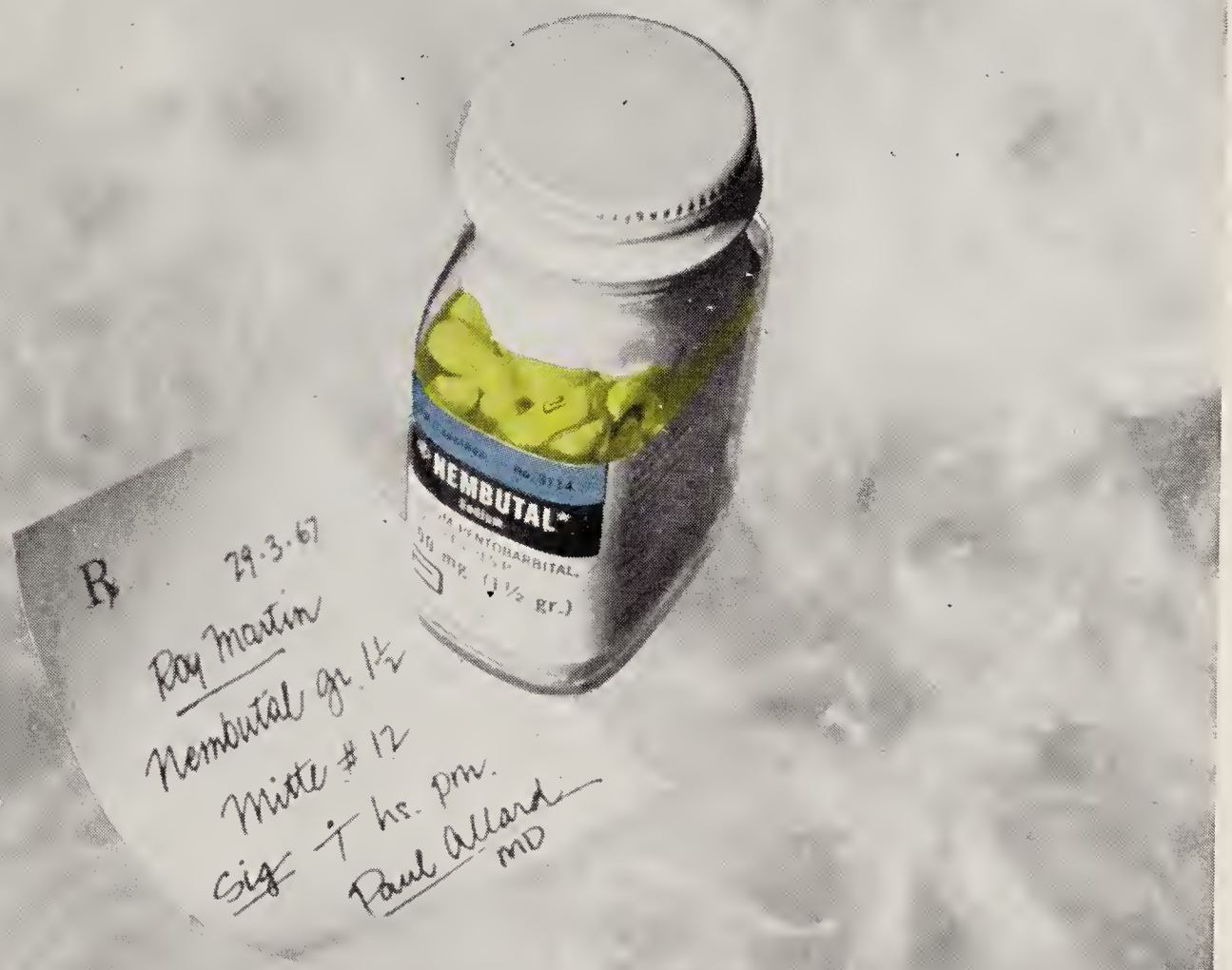

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